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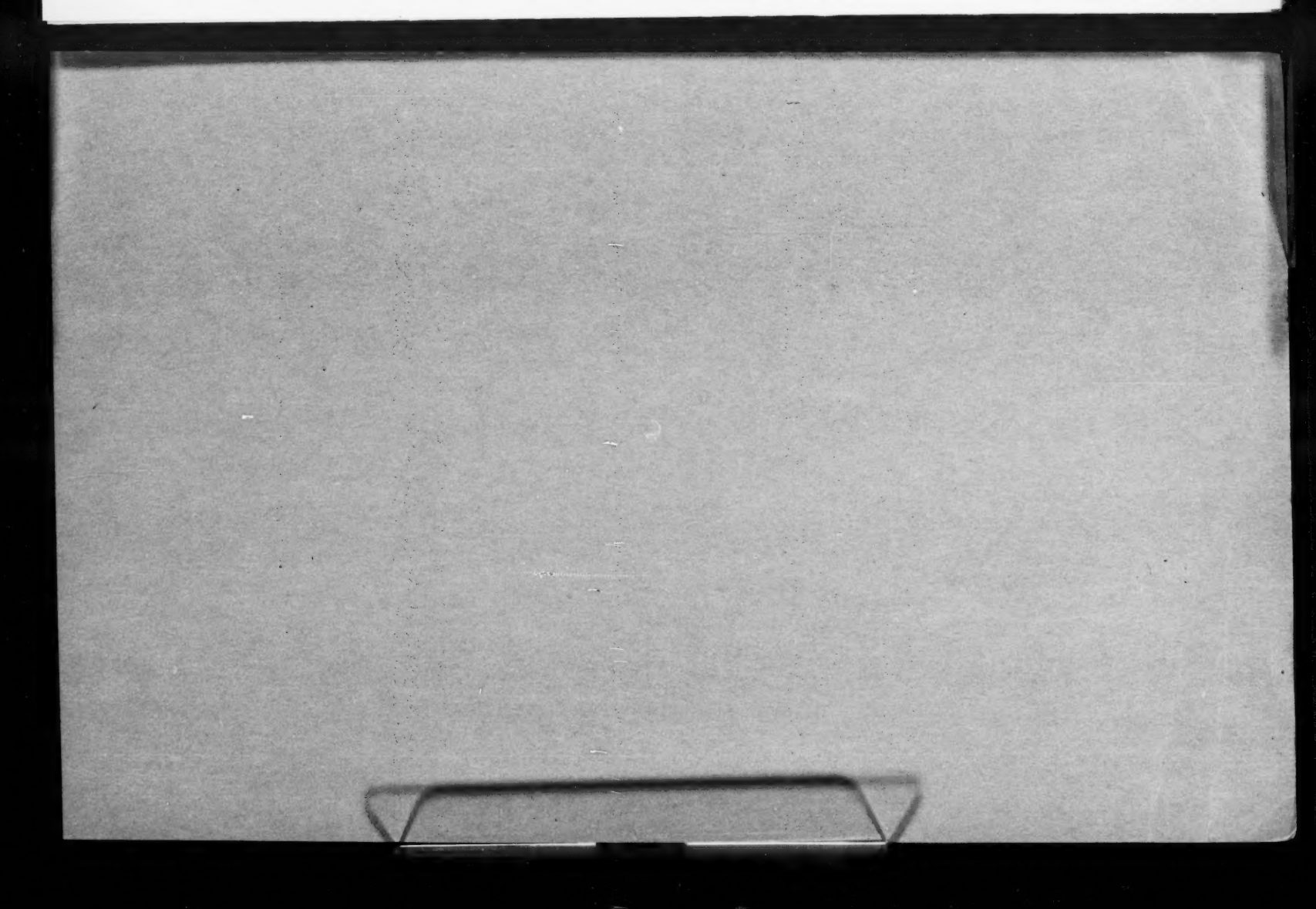

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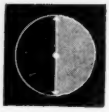

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(1) Joslin, E. P.: Postgraduate Med. 4:302 (Oct.) 1948. (2) Kemper, C. F.: Rocky Mountain M. J. 45:1092 (Dec.) 1948. (3) Pollack, H.: New York Med. 4:15 (Dec. 5) 1948.

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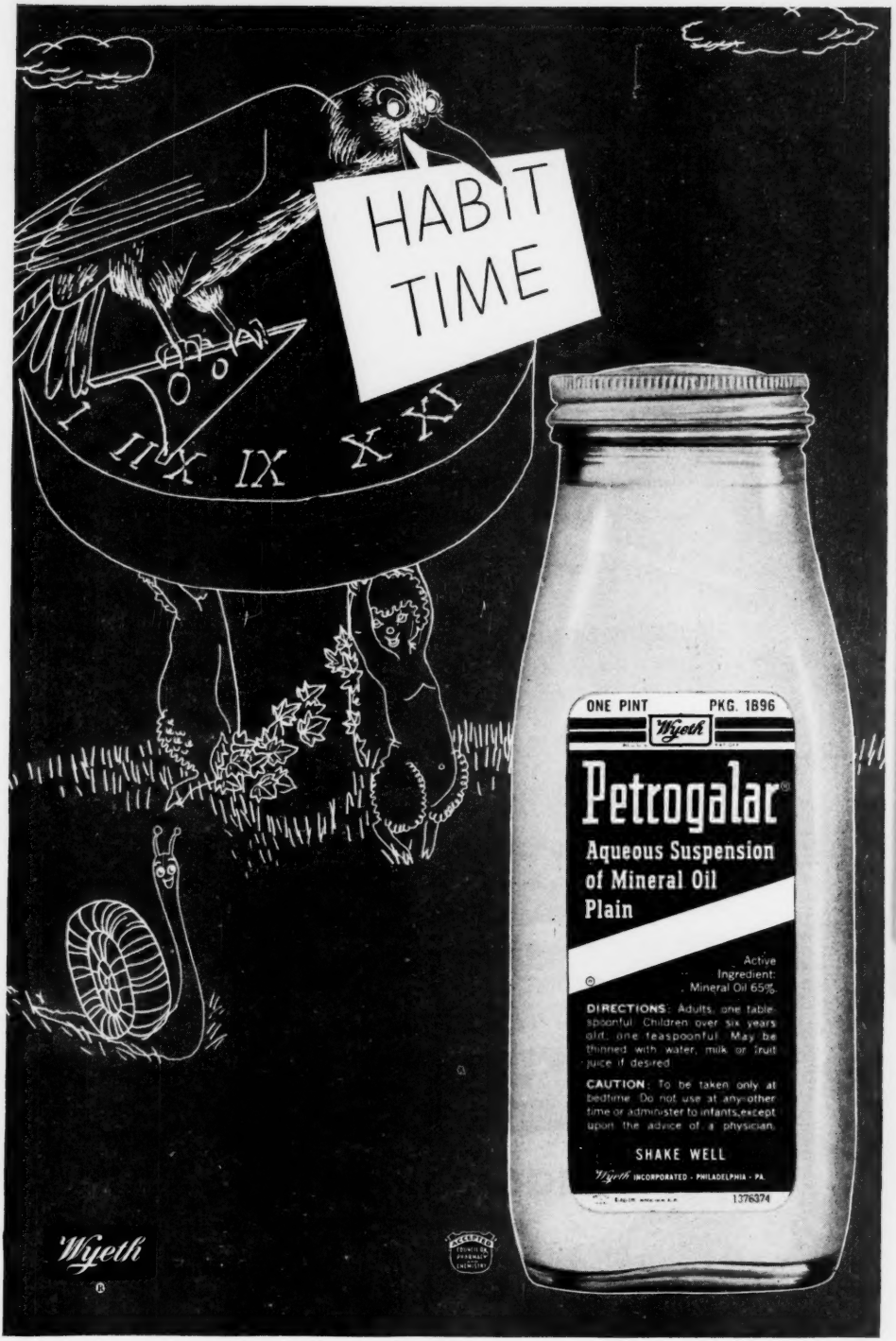
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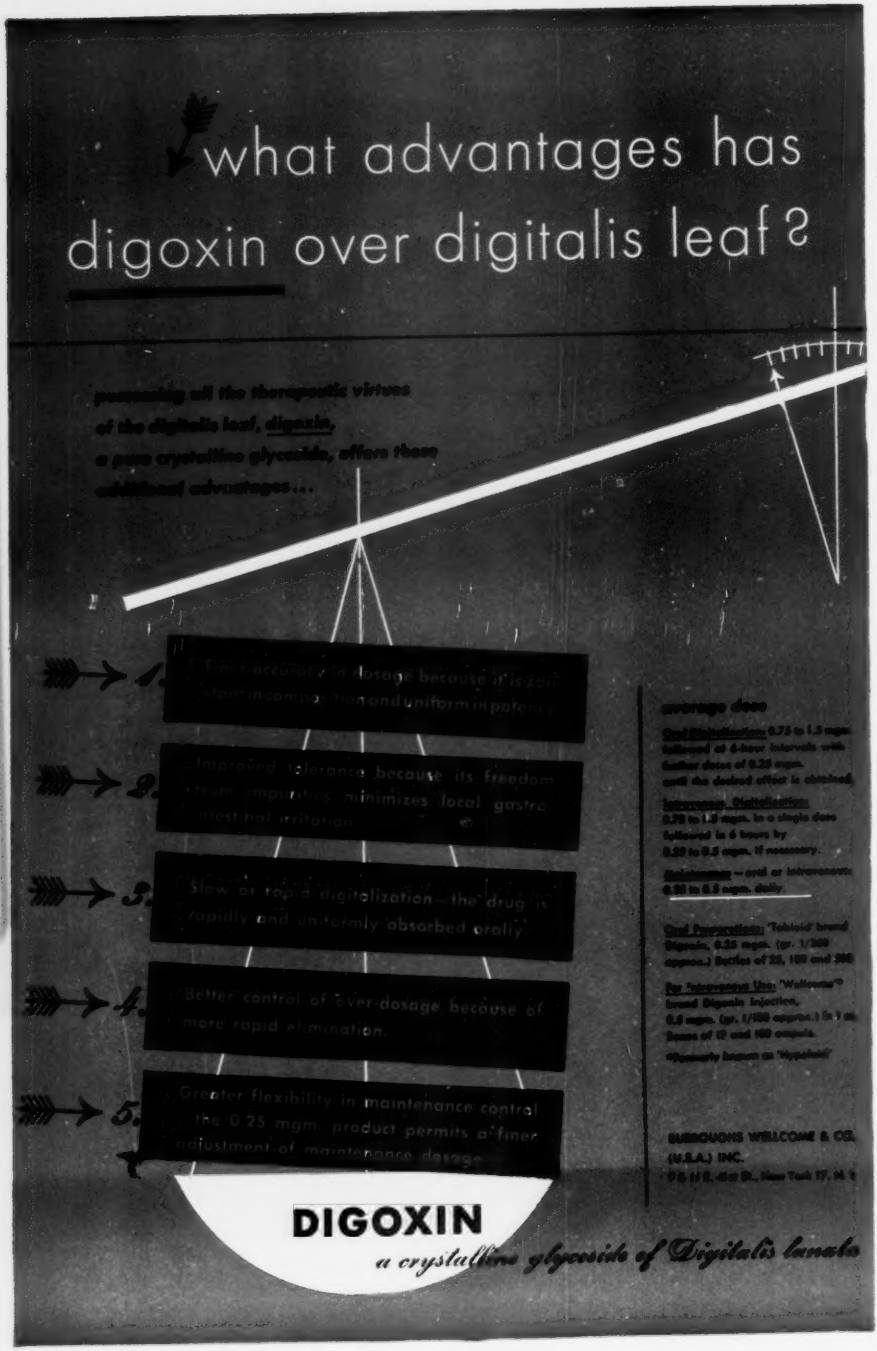
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THE ATAXIAS

A Review

DAVID FISKE, M.D.

LOS ANGELES

CLASSIC descriptions of the ataxias in textbooks are short and convincing, comprising two or three paragraphs, and frequently giving the impression that all of importance is known and well established. Certain "classic, pathognomonic" characteristics are described, with the knowledge of which one can make the diagnosis infallibly: For example, Friedreich's toe indicates Friedreich's ataxia; the Charcot triad, multiple sclerosis. Whereas a certain amount of dogmatism is necessary and may even be justifiable for didactic purposes, the fact remains that a false sense of security is established in an effort to avoid controversial issues.

Examination of the literature discloses considerable confusion concerning ataxia. The confusion is further emphasized by the absence of an adequate review of the subject.

It is felt, therefore, that the present attempt to summarize some of the pertinent data in the literature and associated efforts to simplify the classification of ataxia may be of help to the nonspecialist.

A further point for consideration is the relative importance of rare ataxias. Frequency of incidence alone is not by any means the only criterion of importance. It is the understanding of the rare concept that may well be, and often is, the basis for progress in far more practical fields.

Though one is not generally accustomed to thinking in such terms, there are, in reality, many types of ataxia. This becomes evident when one considers the definition and derivation of the word. A is a privative prefix, and *tassein* means to order or arrange; therefore, "ataxia" means simply "disorder," and for medical purposes the word means disorder or incoordination of the organism.

From the Department of Medicine, Wadsworth General Hospital, Veterans Administration Center.

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A list of the ataxias illustrates the complexity of the problem:

I. Primary Ataxias

A. Friedreich's ataxia (hereditary sclerosis, spinal form)
B. Marie's ataxia (hereditary cerebellar ataxia)
C. Déjerine-Thomas ataxia (olivopontocerebellar atrophy)
D. Foix-Alajouanine ataxia (corticocerebellar atrophy)
E. Multiple sclerosis

II. Secondary Ataxias

A. Locomotor ataxia due to syphilis (tabes dorsalis)
B. Ataxia associated with pernicious anemia, leukemia or aplastic anemia
C. Ataxia associated with pellagra, diabetes or other nutritional disorders
D. Ataxia associated with chronic ergot poisoning
E. "Alcoholic" ataxia
F. Ataxia associated with tumors of the central nervous system

III. Miscellaneous Ataxias

A. Huntington's chorea (hereditary chronic progressive chorea)
B. Sydenham's chorea
C. Parkinsonism (paralysis agitans)
D. Vestibular ataxia
E. Other ataxias

PHYSIOLOGY

Some physiologic considerations may help to elucidate the mechanism which causes ataxia. It has long been known that there is a similarity between the labyrinthine functions and those of the cerebellum. When the cerebellum is removed, the righting reflexes of an organism are exaggerated.[1] Blindfolding a decerebellate dog does not seriously impair its orientation when it swims. This is not the case with the labyrinthectomized animal; it drowns.

Between 1893 and 1906, Kreidle, working with newly molted Palaemontes (shrimp) without otoliths, observed that putting them in filtered water which contained iron filings caused the animals to move subsequently in response to both gravity and magnetism. When such animals were maintained without otoliths of any kind, they were unable to demonstrate any tendencies toward equilibrium.[2]

Prentiss showed that surgical extirpation of one ear vesicle resulted in circular movements, with recovery in about ten days. Streeter carried the process further, removing both vesicles, and noted that there was no recovery of equilibrium. Streeter also showed that the semicircular canals are not essential to the maintenance of equilibrium: well developed equilibrium is present in tadpoles before the existence of definitive canals. Deaf-mute persons are characteristically immune to dizziness, as was pointed out by William James in 1882.[3]

The part that the cerebellum plays in the maintenance of equilibrium, or "order," is apparently that of the central organ of coordination and timing of the body. These functions it accomplishes via the spinocere-

1. Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, ed. 4, Baltimore, Williams & Wilkins Company, 1945.

2. Edwards, A. S.: Measurement of Static Ataxia, Am. J. Psychol. **55**:171, 1942.

3. James, W., cited by Edwards.[2]

bellar tracts and the dorsal fasciculi of the spinal cord, as the afferent limbs, and via the cerebellorubrospinal path, as the efferent limb, cerebral influence being maintained through the corticopontocerebellar path. The general character of the last two paths is well known, despite the lack of detailed information about them. The afferent limbs traverse the spinal ganglions, from terminations in skin, bones, joints, tendons and muscles, by the following routes: (1) to the nucleus dorsalis, from whence fibers go via the dorsal spinocerebellar tract of the same side (some fibers go via the dorsal spinocerebellar tract of the opposite side), through the restiform body (inferior cerebellar peduncle) to the vermis of the cerebellum; (2) to the posterior gray column, through the ventral spinocerebellar tract and the brachium conjunctivum (superior cerebellar peduncle) to the vermis of the cerebellum, or (3) through the posterior funiculus to the nucleus gracilis and the cuneate nucleus and then, as external arcuate fibers, to the cerebellar cortex.[4]

Cerebellar disease results in hypotonia, asthenia, fatigability, slowness of movement, intention tremor (due to increased tonus of antagonistic muscle groups), asynergy, decompoistion of movement dysmetria, rebound phenomenon, adiadokokinesis, vertigo, past pointing and nystagmus.

HISTORY

In 1861, Nicolaus Friedreich[5] described a primary, hereditary disease of the spinal cord which caused progressive ataxia, first of the legs and then of the arms, without paralysis of the sphincters or disturbances of the superficial senses. He designated it as a chronic, degenerative atrophy.

In 1893,[6] Marie reviewed 16 cases of a condition which he stated belonged to a different class from Friedreich's ataxia and called it hereditary cerebellar ataxia.

In 1900, Déjerine and Thomas[6] described the pathology of a nonhereditary, nonfamilial type of cerebellar ataxia and called it olivopontocerebellar ataxia.

Several years later, in 1907, Holmes[6] described a familial degeneration of the cerebellum and stated that the majority of progressive cerebellar diseases were forms of olivopontocerebellar atrophy.

PRIMARY ATAXIAS

Friedreich's Ataxia.—The classic form of Friedreich's ataxia is characterized by early onset, usually between the ages of 5 and 14 years

4. Ranson, S. W.: The Anatomy of the Nervous System, ed. 5, Philadelphia, W. B. Saunders Company, 1935.

5. Friedreich, N., cited by Woofter and Parks.[10]

6. Cited by Gray, R. C., and Oliver, C. P.: Marie's Hereditary Cerebellar Ataxia (Olivopontocerebellar Atrophy), Minnesota Med. **24**:327, 1941.

(though onset may occur at any age), with slow progression, so that patients may reach an old age. Rarely, there may be long remissions. There is usually a definite family history of the disease, though this factor is not invariable. The disease is one of the spinal cord, but it is not limited to a particular tract or set of tracts. Pathologically, there is a combined degeneration of the posterior and lateral funiculi, which is similar to that in the combined sclerosis of pernicious anemia; the difference is that the latter is subacute, whereas the former is chronic.[7] The anatomic changes are such that one cannot say whether one is dealing with Friedreich's ataxia, locomotor ataxia due to syphilis or subacute combined sclerosis of pernicious anemia.

The incidence of the disease is greater in males than in females. Friedreich's ataxia has been described by Turner and Roberts[8] as a sex-linked recessive character. It has usually been considered a non-sex-linked recessive trait.

The onset commonly follows an injury (Litchfeld[9] described a case in which onset followed typhoid) and is manifested in the patient's stumbling while walking or running, due to involvement of proprioceptive fibers. The Romberg sign is present. The disease can be differentiated from the locomotor ataxia of syphilis by the absence of tabetic crises, Argyll Robertson pupil, girdle sensations and a positive reaction to the Wassermann test.[10] The characteristic deformity of the feet, with dorsiflexion of the proximal phalanx of the great toe, plantar flexion of the distal phalanx and exaggeration of the longitudinal arch, is attributed to involvement of the lateral columns, as is the occasional fixation of both ankles. Scoliosis is a frequent finding. Amyotrophic lateral sclerosis may cause pes cavus, but this sign should offer no difficulty in the differential diagnosis because in this condition the onset is in the upper extremities, rather than in the lower, with atrophy of the thenar and hypothenar eminences and the shoulders. There are also muscular twitchings and an absence of familial history in amyotrophic lateral sclerosis. Because of the persistence of the Babinski sign in Friedreich's ataxia, this reflex cannot be tested for. Late in the course of the disease there may be loss or diminution of the knee jerks, owing to the degeneration of fibers proximal to the sensory ganglions, with interruption of the reflex arc.[10] Malone[11] ascribed the persistence

7. Hassin, G. B.: Friedreich's Ataxia: A Histopathologic Study, Arch. Neurol. & Psychiat. **39**:116 (Jan.) 1938.

8. Turner, E. V., and Roberts, E.: A Family with a Sex-Linked Hereditary Ataxia, J. Nerv. & Ment. Dis. **87**:74, 1938.

9. Cited by Turner and Roberts.[8]

10. Woofter, A. C., and Parks, B. S.: Friedreich's Ataxia, Ann. Int. Med. **17**:744, 1942.

11. Malone, W. H.: Friedreich's Ataxia, M. Bull. Vet. Admin. **13**:264, 1937

of the Babinski reflex to involvement of the posterior columns. He described the Babinski sign and "other evidence of pyramidal tract involvement," together with the persistence of superficial abdominal and cremasteric reflexes.

With increased involvement of the direct cerebellar tracts, tremor of the upper extremities and of the head appears. Friedreich emphasized the absence of superficial sensory disturbances and of disturbances of control of the sphincters. Osnata [9] described "great muscular weakness, atrophy and changes in sensation." Lipson and DeNardi [12] confirmed the occasional presence of sensory changes and also described nystagmus and speech defects; there may be associated spina bifida. Mentality is unimpaired in true cases, though Akelaitis [13] described a case in which mental changes occurred, with steady progression to death in two years.

As indicated previously, other conditions, such as pernicious anemia, aplastic anemia, leukemia, diabetes, pellagra, syphilis and chronic ergot poisoning, may produce posterior and lateral funicular involvement. In these secondary ataxias there are no skeletal deformities.

Woofter and Parks [10] described the pathologic changes as hypoplasia of the spinal cord, with degenerative changes involving the fasciculus gracilis and the fasciculus cuneatus, followed by involvement of the pyramidal tracts, the nucleus dorsalis, the ascending cerebellar tracts and, to a variable degree, the cerebellum itself. There are various secondary manifestations, such as thickening and adhesions of the pia mater, particularly near the posterior funiculi, and thickening of the walls of the blood vessels. Numerous whorls of neuroglia are present in the posterior fasciculi, pyramidal tracts, cerebellar tracts and fibers from the posterior roots to the anterior horn cells, causing interruptions of the simple reflex arc.

In this connection, Pitts [9] stated the belief that the prime etiologic factor in Friedreich's ataxia was an inherent tendency to early vascular degeneration, whereas Campbell [9] stated that he believed the process to be the result of faulty development of the posterior fasciculi, with secondary compensatory hyperaction of the lateral tracts and degeneration due to overwork. To Gowers [9] is owed the term "abiotrophy," indicating an inherent tendency to early nerve decay. There are no laboratory findings significant of Friedreich's ataxia. Treatment consists in surgical correction, education and symptomatic care.

Marie's Ataxia and Ataxia of Déjerine and Thomas.—Marie's ataxia may be considered concurrently with the ataxia of Déjerine and Thomas, the difference being chiefly in the hereditary factor.

12. Lipson, H. A., and DeNardi, J. M.: Friedreich's Ataxia: (Familial Hereditary Study of Three Cases), Dis. Nerv. System **7**:261, 1946.

13. Akelaitis, A. J.: Hereditary Form of Primary Parenchymatous Atrophy of the Cerebellar Cortex Associated with Mental Deterioration, Am. J. Psychiat. **94**:1115, 1938.

Onset occurs at from 5 to 60 years of age, usually in adult life, and the illness may last many years. After a gradual onset, with difficulty in walking and lancinating pains in the lower extremities (similar to those in locomotor ataxia due to syphilis), there occurs a progressive ataxia of the upper extremities. There are frequently speech difficulties. The state of the knee jerk may vary from hyperactivity to absence, and spasticity may occur, as may choreiform movements, twitchings and sensory disturbances. There may be remissions of many years' duration.[14] The various findings in these two conditions, it will be noted, have all been described as characteristics of Friedreich's ataxia. Therefore, except for hereditary factors, no clinical distinction can be made between heredocerebellar ataxia of Marie, olivopontocerebellar atrophy of Déjerine and Thomas, cerebellar cortical atrophy of Foix and Alajouanine and Friedreich's ataxia, because the manifestations are common to all. Davison[15] pointed out that a hereditary factor is present even in about one-half the cases of olivopontocerebellar atrophy.

Marie's heredocerebellar ataxia is described as a non-sex-linked dominant character. It has been stated that in general the cerebellar ataxias, when hereditary, are dominant, whereas the spinal variety of ataxia is recessive.

Archambault[16] stated that one must avoid grouping all these ataxias together, for to do so is to defeat the goal of separation of various entities. Davison and Wechsler[6] stated agreement. Hassin and Harris,[17] after pathologic study, stated that there is no microscopic difference of significance between Marie's hereditary cerebellar ataxia and Déjerine-Thomas nonhereditary olivopontocerebellar ataxia, the hereditary factor being the only clinical difference. With this opinion, Waggoner, Loewenberg and Speicher[14] stated their agreement. Hassin,[7] in another histopathologic study, concluded that Friedreich's ataxia and Marie's ataxia are two different morbid conditions: The medulla, pons and cerebellum are not involved in the former, since it is a disease of the fiber tracts, whereas the latter does show such involvement, being a disease of certain groups of ganglion cells, and may, in addition, involve the fiber tracts. Hassin stated,[18] "the clinical difference between cerebellar

14. Waggoner, R. W.; Loewenberg, K., and Speicher, K. G.: Hereditary Cerebellar Ataxia: Report of a Case and Genetic Study, Arch. Neurol. & Psychiat. **39**:570 (March) 1938.

15. Davison, C., in discussion on Waggoner, Loewenberg and Speicher.[14]

16. Archambault, cited by Hassin, G. B., and Harris, T. H.: Olivopontocerebellar Atrophy, Arch. Neurol. & Psychiat. **35**:43 (Jan.) 1936.

17. Hassin and Harris, cited by Nosik, W. A.: Olivopontocerebellar Atrophy (Heredocerebellar Ataxia of Marie) with Encephalographic Findings, Cleveland Clin. Quart. **13**:203, 1946.

18. Hassin, G. B.: Marie's Ataxia (Olivopontocerebellar Atrophy): Clinical and Pathologic Considerations, Arch. Neurol. & Psychiat. **37**:1371 (June) 1937.

atrophy and multiple sclerosis . . . is usually conjectural." He applied the statement to both the hereditary and the nonhereditary forms of cerebellar atrophy. Also, Brower[19] observed that Friedreich's ataxia and multiple sclerosis may be very similar or even the same disease.

A number of variants of the foregoing hereditary forms of ataxia, which do not fit easily into the classifications used, are described in the literature.[20]

Multiple Sclerosis.—Multiple sclerosis is a chronic, progressive disease of the central nervous system, with onset occurring usually between the ages of 20 and 40. It is characterized by the gradual onset of transitory phenomena, such as paresthesias in the lower extremities and scotomas; these are followed by more permanent changes, such as ataxia and tremor in the upper extremities, ocular signs, disturbances of speech, retrobulbar neuritis, pyramidal signs, frequently, and emotional disturbances, ranging from euphoria through pseudobulbar palsy to frank psychosis and complete dementia. There may be bitemporal pallor of the optic disks and absence of abdominal reflexes. The traditional triad of Charcot (nystagmus, intention tremor and scanning speech) may be present and is helpful in making a diagnosis of the disease. The pathologic process consists in the presence of numerous patches of sclerosis and in degeneration of the myelin sheaths. The posterior fasciculi are most frequently involved, though the pyramidal tracts rarely escape, owing to their great length. The remissions, sometimes very long, are due to the fact that the integrity of the axis-cylinders is maintained in spite of the demyelinating process. The cerebellum is usually not involved. It has been established fairly well that heredity, syphilis and trauma play no part in the etiologic process of multiple sclerosis. The disease may be precipitated by pregnancy. Various etiologic factors have been suspected, including toxins, deficiencies, infections and allergy.

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19. Brower, cited by Hall, G. W., and Mackay, R. P.: Forms of Familial Ataxia Resembling Multiple Sclerosis: Clinical Study, Arch. Neurol. & Psychiat. **37**:19 (Jan.) 1937.

20. Ross, A. T.: Combination of Friedreich's Ataxia and Charcot-Marie-Tooth Atrophy in Each of Two Brothers, J. Nerv. & Ment. Dis. **95**:680, 1942. Arieff, A. J., and Kaplan, L. A.: Cerebellar Type of Ataxia with Cerebral Signs, ibid. **100**:135, 1944. Jones, A. B.: A Family of Familial Claw-Foot, M. Clin. North America **11**:325, 1927. Halpern, L.: Ataxia of the Legs and Loss of Vibration: An Isolated Spinal-Syndrome, J. Nerv. & Ment. Dis. **104**:474, 1946. Tureen, L. L.: Schilder's Disease or Friedreich's Ataxia: A Clinical Pathological Study of a Case with Extensive Selective Fiber Tract Lesions, Tr. Am. Neurol. A. **66**:198, 1940. Yang, C. S.; Ling, M. Y., and Chang, S. L.: Hereditary Ataxia: Familial Occurrence in Five Generations, Chinese M. J. **53**: 161, 1938.

Boyd [21] stated the opinion that the disease is almost certainly an infectious process, since the lesions are "identical to acute infectious encephalitis." He described it as an inflammation, with the blood vessels surrounded by collars of lymphocytes and plasma cells. Evidence of inflammation is lacking in the late stages. The various types of ataxia are compared in the table.

It must not be forgotten that of the aforementioned diseases, multiple sclerosis is probably the commonest; the others are rare.

SECONDARY ATAXIAS

The various secondary ataxias are not unique in their symptomatology. Since they are associated with other clinical syndromes, they leave the realm of conjecture and may be spoken of more dogmatically

Characteristics of Four Types of Ataxia *

Friedreich's Ataxia	Marie's Ataxia	Multiple Sclerosis	Déjerine-Thomas Ataxia
Early onset	Late onset	Usually late onset	Usually late onset
Hereditary	Hereditary	Nonhereditary	Nonhereditary
Decreased or missing deep reflexes	Persistent or exaggerated reflexes	Persistent reflexes	Reflexes may or may not be present
No optic signs (Giddings, G.: J. A. M. A. 89: 1396 [Oct. 22] 1927)	Optic signs frequent	Optic signs frequent	Optic signs frequent
No sensory disturbances	Sensory disturbances	Sensory disturbances	No sensory disturbances
Foot deformity	No foot deformity	No foot deformity	No foot deformity
No urinary disturbances	Urinary disturbances	Urinary disturbances	No urinary disturbances
Tendency to spare pyramidal tracts	Pyramidal tracts may be involved	Pyramidal tracts may be involved	Pyramidal tracts may be involved

* The characteristics are merely guides based on the usual descriptions of these ataxias. As mentioned in the text, the characteristics are extremely variable and overlap considerably.

as secondary to the primary disease process. The pathogenesis is, nonetheless, still obscure.

Locomotor Ataxia and Toxic and Nutritional Ataxias.—Locomotor ataxia is generally considered to be secondary to syphilis. While there are certain characteristics of this type of ataxia, it may be secondary to disease processes other than that of syphilis. There are some who say that locomotor ataxia is always due to syphilis, reserving the term "pseudotabes" for the locomotor ataxias of other etiologic processes. These authorities are willing to concede that the reaction to the Wassermann test in the cerebrospinal fluid is positive in only 90 to 95 per cent of cases and the reaction to the Wassermann test of the blood in only about 50 per cent. However, ataxia can be said to be secondary to syphilis only when syphilis can be shown to exist; it cannot be said that syphilis exists because of the presence of so-called tabes dorsalis.

21. Boyd, W.: Textbook of Pathology, ed. 3, Philadelphia, Lea & Febiger, 1938.

The so-called true tabes dorsalis generally makes its appearance from five to fifteen years after the original syphilic infection, but it has been known to occur after only fourteen months. The apparently unique characteristics of locomotor ataxia due to syphilis are sharp, shooting, lancinating pains in the lower extremities, in the buttocks and about the abdomen. They may involve the chest, the arms or even the fifth cranial nerve. These findings, however, have been described in ataxias of other causation.[22] The symptoms mentioned are of variable duration, with involvement of symmetric roots, causing girdle sensations. They may be mistaken for indications of neuritis, arthritis, phlebitis, pleurisy, angina, an acute abdominal condition or hysteria.

Frequently, in patients with syphilitic locomotor ataxia, there are disorders of the bladder; these are, first, retention, followed with overflow incontinence and then automatic emptying. There may be rectal incontinence and diminished or lost libido. All these disturbances are due to involvement of the lowest segments of the spinal cord. Visual disturbances are common. They are diplopia, dimness of vision, pupillary disturbances and atrophy of the optic nerve. Other cranial nerves may be involved by the syphilitic meningitis, causing deafness or facial palsies. Paresthesias are common. The existence of various "crises" is not uncommon (for example, gastric and enteric crises); their mode of production is not known. Locomotor ataxia itself is late in appearing, and is due to involvement of the posterior fasciculi. Other late manifestations are trophic changes: perforating ulcers of the soles and Charcot joints, involving the knees, hips, ankles and lumbosacral joints.

On physical examination there appear the loss of deep reflexes of the lower extremities and sometimes of the upper extremities, disturbances of sensation in the areas of subjective pain and disturbances in the vibration and position senses, with the presence of the Romberg sign.

As previously mentioned, syphilitic tabes may be confused with pseudotabes (so-called), caused by combined sclerosis, diabetes, diphtheria, multiple neuritis or similar conditions. The juvenile form of syphilitic tabes may be confused with Friedreich's ataxia. After therapy for syphilis the signs rarely regress, though involvement of the cranial nerves may clear up.

It is of interest that syphilitic tabes rarely occurs in a fat person. In this connection, Anderson and Pringle [22] described 3 significant cases of gastrointestinal ataxia, complete to girdle sensations and shooting pains in the legs. In 1 case, a large, dilated, kinky bowel, with neither gastric nor duodenal lesions, and a mechanical obstruction of the jejunum

22. Anderson, J. B. M., and Pringle, J. H.: Is There a Gastro-Intestinal Ataxia? Glasgow M. J. **16**:31, 1940.

were observed at operation. With relief of the obstruction and medical management other than treatment for syphilis, there was complete regression of the neurologic symptoms except for persistence of ankle clonus. In the second case, that of a heavy drinker with a retroperitoneal sarcoma, regression of the neurologic findings also occurred under medical and surgical management. The third case was one of carcinoma of the pylorus, with equally good neurologic regression after therapy. In these 3 cases, though they may have been associated with syphilis, since treatment was given prior to the routine determination of the Wassermann reaction of the blood, the significant factor was that the ataxia cleared up after treatment of the gastrointestinal pathologic factors and without treatment for syphilis.

Another interesting observation regarding the specificity of syphilitic locomotor ataxia is that of Orr and Rows [23]; they observed that when celloidin capsules containing bacteria were placed in contact with afferent nerves the toxins apparently passed along the perineural lymphatics and produced degeneration of the posterior fasciculi, indistinguishable from that of syphilitic tabes.

Merritt, Romano and Michael [24] described 5 cases of cortical cerebellar atrophy, in which the only etiologic factor known was that of addiction to alcohol. Wintrobe, Miller and Lasio,[25] too, studied the relation of diet to the occurrence of ataxia. They observed changes in the nervous systems of growing pigs on a deficient diet. The ataxia resulting in the animals was associated with lesions in the peripheral nerves, spinal ganglions, posterior roots and dorsal funiculi. Inanition alone was apparently not the cause, nor was the ataxia due to a deficiency of vitamin A or E, thiamine, riboflavin or nicotinic acid. Of importance was an unknown factor in liver and yeast.

Combined system disease, or subacute combined sclerosis, is another instance of a dietary form of ataxia which has a firmer foothold than some of the types mentioned previously. It usually occurs in pernicious anemia, generally after the anemia is apparent clinically, but sometimes before there are peripheral hematologic changes. The onset is indicated by paresthesias in the fingers and toes, followed by ataxic gait, due to involvement of the posterior fasciculi, and by spasticity of the lower extremities, due to involvement of the pyramidal tracts. There may be sphincteral disturbances and even girdle sensations late in the disease.[26]

23. Orr and Rows, cited by Boyd.[21]

24. Merritt, H. H.; Romano, J., and Michael, M.: Alcoholic Cerebellar Degeneration, Tr. Am. Neurol. A. **66**:195, 1940.

25. Wintrobe, M. M.; Miller, J. L., and Lasio, H.: Relation of Diet to the Occurrence of Ataxia and Degeneration in the Nervous System of Pigs, Bull. Johns Hopkins Hosp. **67**:377, 1940.

26. Musser, J. H.: Internal Medicine, ed. 3, Philadelphia, Lea & Febiger, 1938.

Ocular changes are rare. Combined sclerosis has been observed with severe secondary anemia, with the severe cachexia of pansinusitis and with leukemia, among other conditions.

Ataxia Associated with Tumors.—More discrete lesions, that is, tumors, may also cause ataxia. Lesions of the medulla usually cause ataxia associated with a dissociation of sensation, in which the senses of pain and temperature are usually affected. This type is due to a lesion in the retro-olivary reticular substance and can be produced only by a small lesion involving the arcuate fibers of the bulbothalamic tract, which pass from the gracile and cuneate nuclei to the piriform decussation, or by a lesion of the nuclei. Such lesions have not been produced experimentally, but David and Askenasy [27] reported just such a small lesion of the nucleus of Goll and that of Burdach, caused by the removal of a hemangioblastoma of the medulla.

A prefrontal lesion may produce signs of cerebellar ataxia. This is accomplished through the projection fibers of the frontopontile bundle, extending through the brachium pontis to the opposite side of the cerebellum. The diagnosis may be made by the "dissociation phenomenon," which is an irregular distribution of cerebellar signs.[28]

OTHER ATAXIAS

The ataxia of Parkinson, which is due to involvement of the basal ganglions, is of unknown cause. It is frequently observed after encephalitis and in patients with arteriosclerosis.

The chorea of Sydenham and that of Huntington are also due to involvement of the basal ganglions, the former being attributed to the generalized pathologic process of rheumatic fever or collagen disease, and the latter being a familial disease.

Another ataxia with involvement of the basal ganglions is progressive lenticular degeneration (hepatolenticular degeneration), described by Wilson in 1912.[29] It is an uncommon condition, familial in nature, and usually appears in persons under 30. The clinical manifestations are usually bilateral, athetoid movements of the hands, arms, legs and face. The limbs are spastic and often end in contractures. The spasticity is not due to involvement of the pyramidal tract; consequently, though the deep reflexes are active, there are absence of the Babinski sign and persistence of the superficial abdominal reflexes.[30] Sensation

27. David, M., and Askenasy, H.: Ataxia and Astereognosis of Bulbar Origin, Brain **60**:354, 1937.

28. Gordon, A.: Further Contribution to the Subject of Frontal Ataxia, J. Nerv. & Ment. Dis. **90**:614, 1939.

29. Cited by Musser.[26]

30. Cecil, R. L.: A Textbook of Medicine by American Authors, ed. 5, Philadelphia, W. B. Saunders Company, 1942.

is unaffected. True paralysis is not present,[31] nor is actual muscular weakness, but, owing to the rigidity and contractures, there is an apparent weakness. Dysarthria and dysphagia are frequent. The facial hypertonicity results in a spastic smile and in involuntary emotionalism. The disease is progressively fatal in a few years. There is no known treatment.

Sometimes the extremities are involved with a slow, rhythmic tremor of the type of paralysis agitans, but different in that it is increased by voluntary movement. This form of the disease is known as pseudosclerosis; and, though it is sufficiently different clinically to be misdiagnosed as multiple sclerosis or postencephalitic parkinsonism (particularly since it occurs more frequently in somewhat older patients), it has been shown by Hall to be a variety of progressive lenticular degeneration. The characteristic pigmentation of the cornea known as the Kayser-Fleischer ring has been found to be present in all recorded cases of the pseudosclerotic variety of the disease, as compared with an incidence of this sign in 60 per cent of cases of hepatolenticular degeneration. It is not present in any other condition.[31]

Pathologically, the basal ganglions are involved with an extensive degenerative process of unknown cause, sometimes with cavity formation. The condition is associated with a peculiar "hobnail" cirrhosis of the liver, of mixed type. The peculiar tremor probably results from degenerative changes, almost constantly present, in the dentate and red nuclei, rather than from the lesions of the basal ganglions. The association of the hepatic cirrhosis and the cerebral lesions, though close and frequent, is not absolute. A case of progressive lenticular degeneration unassociated with hepatic cirrhosis was described by Uzman and Denny-Brown.[32] A nonspecific increase in the amino acids in the urine led these authors to the belief that the disease may be an inherent error of amino acid metabolism.

Ménière's syndrome is a symptom complex indicative of a disturbance of the labyrinth, due to inflammation or hemorrhage, especially as a result of syphilis or arteriosclerosis. The acute episode, usually due to hemorrhage with complete destruction of the labyrinth, is characterized by intense dizziness, vomiting, profound disturbances of equilibrium with a sensation of rotation of the body around its long axis, and pronounced nystagmus.[30] The patient cannot stand; he lies on the sound side, since turning on his back or onto the involved side causes intense vertigo. The acute episode may be so sudden as

31. Meakins, J. C.: The Practise of Medicine, ed. 3, London, Henry Kimpton, 1942.

32. Uzman, L., and Denny-Brown, D.: Amino-Aciduria in Hepato-Lenticular Degeneration (Wilson's Disease), Am. J. M. Sc. **215**:599, 1948.

to fell the victim. Symptoms are pronounced for four to five days and then subside gradually, but the nystagmus persists for a longer period, and quick turning of the head may produce vertigo. Disturbances of equilibrium eventually pass away, but tinnitus and impaired hearing or deafness remain.

It has been suggested by some authors that when hemorrhage is not the etiologic factor the cause may be similar to that of trigeminal neuralgia. Other etiologic factors may be obstruction of the eustachian tubes, in which case the therapy is release of the obstruction, when possible; increased intracranial pressure, in which case lumbar puncture may be of value, or increased blood volume or vestibular fluid (suggested by Cheatle [29]), for which acid-ash and dehydrating diets have been recommended. In treatment of arteriosclerosis, nicotinic acid in large doses has been of value.

Chronic labyrinthitis is usually secondary to disease of the middle ear. It is not always progressive, but may recur for long periods of time. When mild, the symptoms may be confused with those of petit mal, but the presence of deafness and tinnitus and the absence of complete loss of consciousness suggest labyrinthitis. Relief of symptoms is difficult; section of the eighth cranial nerve has been recommended.

Also to be considered are tumors of the cerebellopontile angle. These generally arise from the sheath of the acoustic nerve. The initial symptoms are tinnitus and vertigo, followed by progressive nerve deafness.[30] In time, there is involvement of the fifth cranial nerve with paresthesias of the face and tongue, followed by involvement of the facial nerve. Finally, there is definite evidence of cerebellar compression, with typical symptoms referable to the cerebellar tract. These tumors grow slowly, and two to five years may elapse before successive involvement of contiguous structures makes the diagnosis evident. Therapy is surgical.

THERAPY

The primary disease to which a secondary ataxia is attributed must be treated specifically, when such therapy is available. Wheeldon [33] reported improvement of "ataxia, athetosis and chorea," but not of spasticity, with the use of snake venomine. The usual treatment is corrective surgery, education and symptomatic therapy.

SUMMARY AND CONCLUSIONS

As one reconsiders the various descriptions, observations and opinions outlined, it may seem that a good deal of hair-splitting exists. Friedreich's ataxia is hereditary, primary, spinal ataxia. Marie's ataxia

33. Wheeldon, T.: Preliminary Observations on the Use of Snake Venomine in the Treatment of Spastic Paralysis, J. Internat. Coll. Surgeons **3**:362, 1940.

is hereditary, primary, cerebellar ataxia. Déjerine-Thomas ataxia is nonfamilial, primary, cerebellar ataxia. Foix-Alajouanine ataxia is primary, cortical, cerebellar atrophy. All the cerebellar ataxias are in the category of olivopontocerebellar atrophy, differentiation being a matter of a familial factor and of degree. The ataxias of pernicious anemia, aplastic anemia and leukemia are considered to be nonhereditary, secondary, spinal ataxia. However, it is known that blood dyscrasia of one kind or another sometimes "runs in families."

To pigeonhole an ataxia as hereditary, or even to give it a name such as "Friedreich's" or "Marie's" ataxia, is undesirable. The practice tends to imply that since the diagnosis has been made and the condition may be hereditary, nothing can be done. It gives a sense of futility. This should certainly not be the case.

One must get down to fundamentals and think of dynamics. Even hereditary diseases, when viewed in the newer light of Beadle's work,[34] may appear in the nature of incomplete metabolic processes, amenable to correction. To assume that heredity alone is enough to account for the onset of a disease in adult life is unreasonable. Even degenerative diseases, inherited or otherwise, must be secondary to some insult. To use the word "abiotrophy" for this process, as does Gowers, is again hiding behind a false sense of security. To name a process is not to explain it.

Perhaps, as is not unlikely, heredity may be responsible for the early onset of degenerative diseases before the chronologic recognition of senility. But this degenerative process may well be controlled by avoiding the precipitating insult. It is the precipitating insult that one must regard as the primary, etiologic factor, clinically speaking. Thus, who is to say that subacute combined sclerosis could not develop in a person without pernicious anemia? It is known to occur in people in whom the hematologic signs of pernicious anemia develop after the onset of ataxia. However, here pernicious anemia is the primary etiologic factor.

The mere fact that primary spinal ataxia generally occurs in children, whereas primary cerebellar ataxia generally occurs in adults, does not necessarily mean that the two are different disease processes, though, to be sure, the possibility exists. Obviously, from the previous descriptions, the various ataxias overlap considerably.

Several examples may help to illustrate this point. Pneumonia may be caused by the pneumococcus, the staphylococcus, the Friedländer bacillus or any one of a number of viruses and bacteria, but the primary pathologic process remains the same. But for different cloth-

34. Beadle, G. W.: Genetic Control of Biochemical Reactions, Harvey Lect. (1944-1945) **40**:179-194, 1945.

ing, pneumonia remains pneumonia. Mumps generally occurs in children. When it does so, the disease process is a parotitis, and not, ordinarily, an orchitis. However, in a minority of cases mumps occurs in adults. When this happens, the pathologic process is still a parotitis, but there may be a superimposed orchitis. The fact that the testis in men seems to have a particular susceptibility to the virus of mumps does not mean that the disease process is not mumps. By the same token, if mumps were to involve any of the other salivary glands, as it frequently does, it should not deter one from making the same diagnosis—mumps.

To be sure, these various ataxias may be different entities, but one is not in the position to say that they are. One must think in terms of fundamental physiology and dynamics and the various possible etiologic factors. Only in this way can one make progress toward the ultimate goal, which should be to understand these disease processes thoroughly, to pigeonhole them correctly and, above all, to treat them more satisfactorily.

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RADIOACTIVE ISOTOPES IN THE STUDY OF PERIPHERAL VASCULAR DISEASE

I. Derivation of a Circulatory Index

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THE APPLICATION of a new investigative tool in medical research is an exciting experience. Old concepts and barriers to new ideas crumble, and new avenues of approach to the understanding and solution of previously impenetrable problems appear. We are reporting on the use of radioactive isotopes in the investigation of peripheral vascular diseases, especially arteriosclerosis obliterans. The gradual aging of the population has increased the incidence of arteriosclerosis and its complications and will undoubtedly continue to do so. One such factor, recently enunciated, has been the progressive development of obliterative vascular diseases in diabetic patients, whose lives have now been prolonged by approximately a generation through the judicious use of insulin. The frequent occurrence of advanced vascular disease among patients at Cook County Hospital and the resulting necessity for amputations prompted this investigation. In the past several years, a number of reports [1] have appeared on the use of various substances to improve blood supply to the extremities, thus preventing or delaying, amputation. Moreover, there has been a definite trend toward

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From the Hektoen Institute for Medical Research, Cook County Hospital, The Peripheral Vascular Clinic, Mercy Hospital, and the Department of Surgery, Stritch School of Medicine of Loyola University.

1. Katz, R. A.: Impending Ischemic Gangrene: New Non Surgical Therapeutic Suggestions (Preliminary Report), New Orleans M. & S. J. **98**:542-555 (June) 1946. Wirtschafter, Z. T., and Widmann, R.: Elaboration of Histamine in Vivo in the Treatment of Peripheral Vascular Disorders: Preliminary Report, J. A. M. A. **133**:604-605 (March 1) 1947. Berry, R. L.; Campbell, K. N.; Lyons, R. H.: Moe, G. K., and Sutler, M. R.: Use of Tetraethylammonium in Peripheral Vascular Disease and Causalgic States: New Method for Producing Blockade of Autonomic Ganglia, Surgery **20**:525-535 (Oct.) 1946

conservation of tissue because of the improved ability to combat infection and nutritional deficiencies. The role of the autonomic nervous system in peripheral vascular conditions has also received recent emphasis. Because the results with all these methods of improving the blood supply to the extremities varied so greatly from patient to patient, we felt that a more fundamental evaluating of the peripheral circulation than that by the means available to us was necessary.

Ochsner and DeBakey,[2] in 1939, listed the then acceptable measures for determining peripheral blood supply as calorimetry, oscillometry, plethysmography and capillary microscopy. Calorimetry is a trying procedure, requiring that the patient maintain his equilibrium in the environment of a constant temperature. Oscillometric readings are apparently inaccurate and were not recommended by Allen and his co-workers.[3] The remaining methods, though more accurate, are cumbersome and difficult to use clinically on large numbers of patients.

Quimby and Smith[4] have recently revived interest in the use of radioactive substances in studying peripheral vascular diseases. Blumgart and others,[5] in 1927, used radium C and the Wilson cloud chamber to measure circulation time. Later that year, an ionization chamber of the type designed by Geiger was used for the detection of radioactivity. McCracken, Essex and Sheard[6] repeated these experiments ten years later; using dogs and a more compact ionization chamber, they determined the effect of anesthesia, temperature and various drugs on the

2. Ochsner, A., and DeBakey, M.: Peripheral Vascular Disease: Classification and Therapeusis Based upon Physio-Pathologic Alterations, Internat. Clin. **3**:1-32 (Sept.) 1939.

3. Allen, E. V.; Barker, N. W., and Hines, E. A., Jr.: Peripheral Vascular Diseases, Philadelphia, W. B. Saunders Co., 1946, p. 380.

4. Quimby, E. H., and Smith, B. C.: Tracer Studies with Radioactive Sodium in Patients with Peripheral Vascular Disease, Science **100**:175-177 (Aug. 25) 1944. Smith, B. C., and Quimby, E. H.: Use of Radioactive Sodium in Studies of Circulation in Patients with Peripheral Vascular Disease: Preliminary Report, Surg., Gynec. & Obst. **79**:142-147 (Aug.) 1944: Use of Radioactive Sodium as Tracer in Study of Peripheral Vascular Disease, Radiology **45**:335-346 (Oct.) 1945. Quimby, E. H.: Radioactive Sodium as a Tool in Medical Research, Am. J. Roentgenol. **58**:741-753 (Dec.) 1947.

5. Blumgart, H. L., and Yens, O. C.: Studies on Velocity of Blood Flow: Method Utilized, J. Clin. Investigation **4**:1-13 (April) 1927. Blumgart, H. L., and Weiss, S.: Studies on Velocity of Blood Flow: Pulmonary Circulation Time in Normal Resting Individuals, ibid. **4**:399-425 (Aug.) 1927.

6. (*a*) McCracken, E. C.; Essex, H. E., and Sheard, C.: Circulation Time of Blood of Dogs, Determined by Ionization (Geiger Counter) Methods: Effects of Physicophysiological Agents and of Drugs, Am. Heart J. **14**:51-59 (July) 1937. (*b*) McCracken, E. C.; Sheard, C., and Essex, H. E.: Ensemble for Determination of Circulation Time of Blood by Ionization (Geiger Chamber) Method, Proc. Soc. Exper. Biol. & Med. **36**:106-110 (March) 1937.

circulation time. In 1942, Hubbard and associates [7] measured the blood flow in infants and children, using artificially prepared radioactive substances. Quimby and Smith used radioactive sodium in their studies. They demonstrated that differences between circulation times in normal persons and in those with arteriosclerosis were not significant. They postulated a difference in "build up" in the curves indicating the rate of accumulation of the isotope in the tissues, varying with the impairment in circulation.

PRESENT INVESTIGATION

Our studies on peripheral vascular conditions began in May 1947, at which time we were able to obtain, through the Atomic Energy Commission, a supply of radioactive phosphorus from the Clinton National Laboratory at Oak Ridge, Tenn. Although previous studies had been made with radioactive sodium, we could find no advantage in this over radioactive phosphorus and continued to use the latter. The purpose of this report is to describe the results of our tests in a series of patients, some normal and some with arteriosclerosis, and to present a mathematical evaluation and comparison of the circulation in normal and in arteriosclerotic extremities. From our studies we have derived an index which we feel has diagnostic and prognostic characteristics. In another publication, we (M T. F., W. J. P.) [8] reported on the use of radioactive phosphorus in studies of arteriosclerosis obliterans treated with histidine and ascorbic acid, and we were able to show that clinical changes in circulation were related to the rate of deposition of P^{32} in the tissues. The significance of this rate of deposition is the chief subject of this report.

Method and Equipment.—Radioactive phosphorus (P^{32}) was obtained in the form of phosphoric acid (H_3PO_4) or sodium phosphate (Na_2HPO_4) in solution. P^{32} is an emitter of beta rays, with a half-life of 14.3 days and an energy value of 1.69 million electron volts per disintegration. Radioactive sodium (Na^{24}) is an emitter of beta and gamma rays, with a half-life of 14.8 hours and an energy value of 2.8 million electron volts per disintegration. The greater difficulty in shielding the gamma rays and the increased energy per disintegration of Na^{24} made radioactive sodium more inconvenient and hazardous to use in clinical investigations. A brief series of trials revealed that results obtained with P^{32} were similar to those obtained with Na^{24} (fig. 5) and the P^{32} was then used exclusively. Possibly the only advantage of the Na^{24} was its shorter half-life. Some P^{32} was retained in the body, but the residual radioactivity did not interfere with any subsequent studies.

7. Hubbard, J. P.; Preston, W. N., and Ross, R. A.: Velocity of Blood Flow in Infants and Young Children Determined by Radioactive Sodium, J. Clin. Investigation **21**:613-617 (Sept.) 1942.

8. Friedell, M. T.; Drucker, E. F., and Pickett, W. J.: Histidine and Ascorbic Acid Treatment of Arteriosclerosis Obliterans, with Radioactive Isotope Estimations of Circulatory Effects, J. A. M. A. **138**:1036-1039 (Dec. 4) 1948.

According to Evans,[9] the amount of radiation to which the body is exposed after the introduction of the radioactive phosphorus can be estimated by the formula:

$$RE = 1.44T(60CE_{av})$$

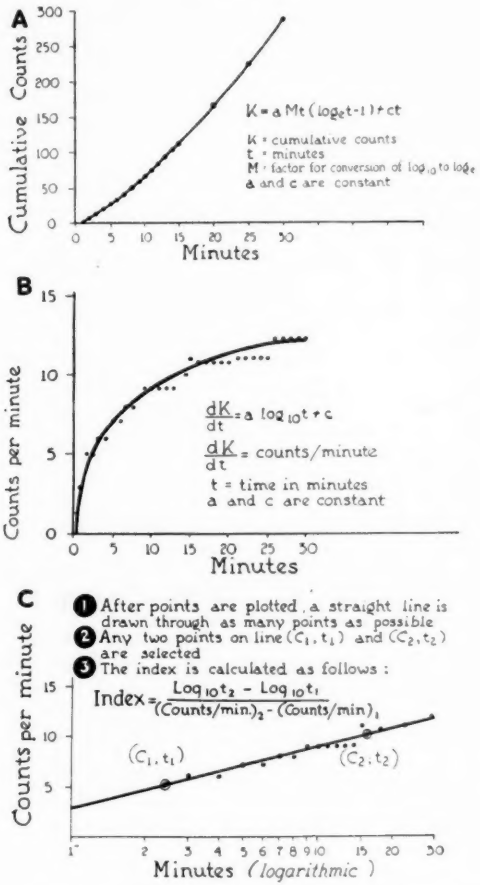

Fig. 1.—*A*, curve of cumulative counts. *B*, curve of counts per minute. *C*, semi-logarithmic plotting of curve of counts per minute.

where *RE* equals roentgen equivalents, *T* half-life in days, *C* concentration of the isotope in microcuries per gram of body weight and E_{av} the average energy per

9. Evans, R. D.: Tissue Dosage in Radio-Isotope Therapy, Am. J. Roentgenol. **58**:754-756 (Dec.) 1947.

disintegration This is the maximum amount of roentgen equivalents which could be absorbed if all the isotope were disintegrated in the tissues. However, about 20 to 40 per cent is quickly excreted by the kidneys. For a 70 Kg. man given an

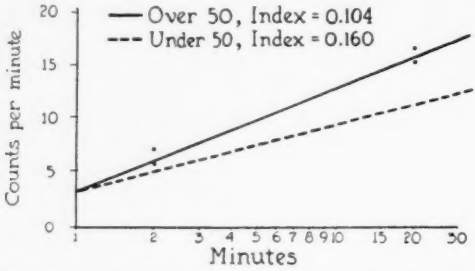

Fig. 2.—Semilogarithmic curves of counts per minute according to ages of patients.

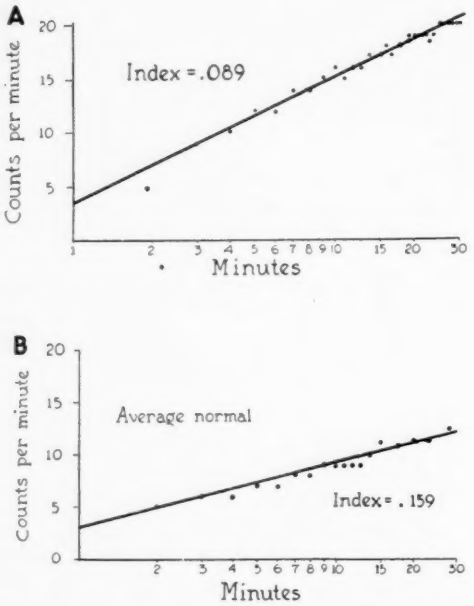

Fig. 3.—*A*, semilogarithmic curve of counts per minute for patients with arteriosclerosis; *B*, similar curve for patients with normal circulation.

injection of 200 microcuries of P^{32} (the usual dose), maximum absorbable radiation with present methods is about 2 roentgen equivalents.

A scaling Geiger-Müller counter with a probe type tube, a synchronized clock and a recording register was used. (This register records 1 unit for every 64 impulses received by the tube, individual impulses being interpolated by flashing neon bulbs arranged in a geometric series.)

A routine method of examination was established in order to limit as much as possible environmental and positional factors. The subject was placed in a recumbent position and the Geiger probe applied to the sole (it was placed directly on the skin and held in place with gauze tape). The register and the clock were set at zero, after a preliminary trial to exclude extraneous radiation. Ten cubic centimeters of isotonic sodium chloride solution containing 200 microcuries of P^{32}, previously prepared and assayed, was injected rapidly into a cubital vein. Counts were then recorded every five seconds for the first minute and every minute for the next thirty minutes. (There is always a background of cosmic radiation; in our laboratory this caused an impulse every few seconds.)

We have found a scale of 1 to 64 to be useful and statistically valid in plotting our data. Thus, all counts cited should be multiplied by 64 to obtain the number of impulses actually received by the counter. When the counts are plotted against time, a characteristic curve is obtained (fig. 1 *A*). The general formula for this curve is stated in figure 1 *A*. We have designated this as the cumulative counts curve. If the counts obtained in each succeeding minute are plotted against time, a curve of the "build-up" type is obtained (fig. 1 *B*). The general formula for this curve is stated in figure 1 *B*. This curve is the first derivative of the cumulative counts curve and represents the diffusion of P^{32} into the tissues. If this curve is plotted on semilogarithmic graph paper on which time is designated logarithmically, the points forming the greater part of the curve lie on a straight line (fig. 1 *C*). This is especially obvious if the first and the last few minutes are disregarded, to allow, respectively, for mixing time and for the fact that diffusion has reached equilibrium. For practical purposes, the straight line which best fits these points is drawn. The slope of this line is definitely related to the rate of diffusion of P^{32} into the tissues; the significance of its variations will be discussed.

Clinical Material.—The data for analysis in this report were obtained from 100 patients in the wards of the Cook County Hospital. Forty-one patients were under 50 years of age, and 49 patients were clinically free from arteriosclerosis. The criterion for the diagnosis of arteriosclerosis was absence of peripheral pulsations in the lower extremities, evidence of compensated arteriosclerotic heart disease, arteriosclerotic encephalopathy or sclerotic changes of the retinal vessels. Of the patients with advanced arteriosclerosis obliterans as evidenced by gangrene, of an extremity, 10 were selected in whom gangrene was confined to one lower extremity.

Mathematical Computations and Data.—As the investigations proceeded, it became obvious that P^{32} concentrated more rapidly in the tissues of the extremities of persons with arteriosclerosis than in the tissues of subjects with apparently normal circulation. When the data obtained were plotted, as previously noted, the slope of the semilogarithmic curve was usually definitely steeper for patients in whom arteriosclerosis was present (fig. 4). Our first problem was to determine whether variations in this slope were significantly different for persons with arteriosclersis and for normal persons. For statistical reasons, the following method of analysis was adopted. After the data obtained from the readings for each patient were plotted on semilogarithmic paper, the best fitting straight line was drawn through the useful portion of the curve. Values were determined for the counts coinciding with the line at the two minute point and at the twenty minute point. This

was done to make the calculation of the slope of the curve as simple as possible (fig. 1C). Again, for statistical reasons, it was found more useful to divide the difference of the logarithms of time by the difference of the counts per minute, thus computing

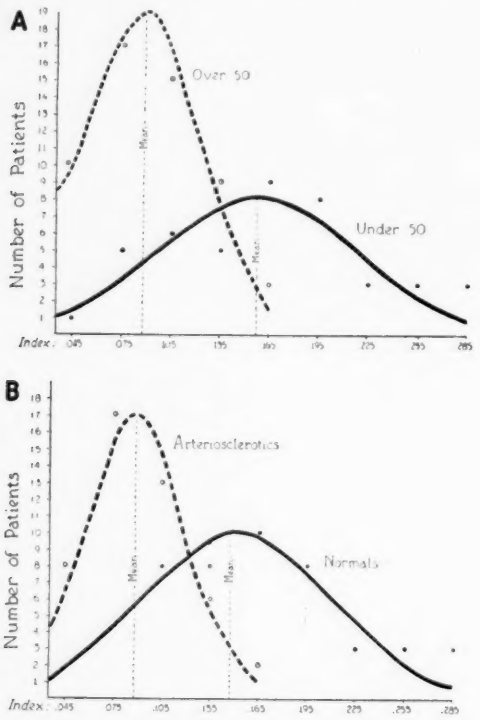

Fig. 4.—*A*, distribution of indexes according to age; *B*, distribution according to state of the arteries.

TABLE 1.—*Classification of Patients According to Age and State of the Arteries*

	No. of Patients	Average Age	Sex		Race		Mean Index	Range of Index		Standard Deviation
			Male	Female	White	Negro		Maximum	Minimum	
Patients under 50.....	41	33.6	39	2	14	27	0.159	0.285	0.050	0.060
Patients over 50.....	59	66.2	53	6	46	13	0.090	0.166	0.035	0.034
Patients with normal circulation.....	49	36.9	47	2	18	31	0.152	0.285	0.047	0.059
Patients with arteriosclerosis.....	51	66.3	45	6	42	9	0.080	0.185	0.035	0.032

the cotangent, or reciprocal of the slope. This allowed us to plot a typical distribution curve. We have designated this quotient as an index of circulation, although we feel that it is limited to one phase of the blood circulation. The formula for this index may be expressed as:

$$\text{INDEX} = \frac{\log T_2 - \log T_1}{\text{Counts } T_2 - \text{Counts } T_1}$$

where T_1 equals two minutes and T_2 twenty minutes and Counts T_1 equals theoretic counts per minute in the second minute and Counts T_2 theoretic counts per minute in the twentieth minute. Since $\log 20 - \log 2 = 1$, the formula becomes:

$$\text{INDEX} = \frac{1}{\text{Counts } T_{20} - \text{Counts } T_2}$$

It must be emphasized that these counts represent one sixty-fourth of the impulses received by the Geiger probe and that they are obtained from the theoretic straight line drawn to fit best, rather than from the actual, crude data obtained experimentally.

This index is also a measure of the rate of diffusion of the P^{32} and values are directly comparable from one time to another. Therefore, it represents a way of

TABLE 2.—*Distribution of Indexes with Theoretic Frequencies of and Goodness of Fit*

	Patients Under 50 Yr.		Patients Over 50 Yr.		Patients with Normal Circulation		Patients with Arteriosclerosis	
Index	No. of Patients	Theoretic Frequency	No. of Patients	Theoretic Frequency	No. of Patients	Theoretic Frequency	No. of Patients	Theoretic Frequency
0.030-0.059	1	1.3	11	8.7	3	1.9	9	7.4
0.060-0.089	5	3.1	17	18.9	5	4.3	17	17.3
0.090-0.119	6	5.5	17	18.9	8	7.2	15	16.7
0.120-0.149	5	7.5	11	8.7	8	9.5	8	6.7
0.150-0.179	9	8.1	3	1.1	10	9.7	2	1.9
0.180-0.209	8	6.8	0	....	8	7.6	0	....
0.210-0.239	3	4.5	..	....	3	4.6	..	....
0.240-0.269	2	2.3	..	....	2	2.1	..	....
0.270-0.299	2	0.9	..	....	2	0.8	..	....
Random samples which produced no better fit, % (determined by chi square).....	86.7		77.0		89.8		89.1	

comparing values for at least one phase of circulation, directly between patients and at various intervals after therapeutic measures are instituted.

The mean circulatory index established for patients under 50 years of age was 0.160, and the mean for patients over 50 was 0.104 (fig. 2). A similar difference was noted between the normal persons and subjects with arteriosclerosis: The mean circulatory index for patients with evidences of arteriosclerosis was 0.089 (fig. 3*A*), and for the normal persons it was 0.159 (fig. 3*B*). Indexes of circulation for patients over 50 and for those with arteriosclerosis fell into well defined groups (fig. 4). Indexes for persons under 50 and for persons with normal circulation also fell into well defined groups; however, these groups had a broader range than those of the older and the arteriosclerotic patients (fig. 4). Because of the biologic nature of the problem, one would expect overlapping of the two groups; this will be considered later. No index was found below 0.035 and none above 0.285 (table 1). The indexes were separated into groups differing by 0.030 (table 2), and these were plotted against frequency of occurrence (fig. 4). It will be seen that these represent normal distribution curves.

The standard deviations and the theoretic frequencies were established and the goodness of the fit was determined by chi square. For the various dis-

tribution curves, from 77 to 89.8 per cent of random samples selected gave no better fit (table 2). The area overlapping was about 10 per cent on the curve of the older group and about 35 per cent on that of the younger group. The same relation was noted between the curves of normal persons and those of patients with arteriosclerosis.

COMMENT

Contrary to our expectations, it was noted that the curves for the older groups of patients and for those with arteriosclerosis established a greater build up than did the curves for groups of younger people and for those with normal circulation. The same trend was indicated among the few patients tested with Na^{24} (fig. 5). This means that the radioactive ion diffused into the tissues at a faster rate in the older patients and in those with abnormal circulation. As stated before, the latter group includes patients with signs and symptoms of advanced arteriosclerosis, even apparently to pregangrenous stages. It is difficult to attribute this increased build-up curve for these patients to an actual increase in blood flow. Since the beta particle emitted by the P^{32} ion can penetrate only a few millimeters of tissue, and since the probe of the counter is applied to the thickened skin of the sole, what is measured is chiefly radioactivity from the ion deposited in the tissues. This implies that P^{32} leaves the capillaries at a faster rate in patients with arteriosclerosis than in normal subjects. The actual quantity of P^{32} injected (200 microcuries) is about 0.005 mg.; this means that approximately 1 in every 10^{13} atoms of phosphorus is radioactive in the body.[6b] This does not affect significantly the concentration of the phosphate ion in the blood. Because the ion is freely diffusible, apparently the only factor to account for variation in the rate of diffusion is the size of the available area of membrane through which diffusion can occur (fig. 6). The rate of diffusion varies with the size of the capillaries. Thus, in persons with arteriosclerosis and in those of advanced age, capillary dilatation is always present.

Ricker,[10] in 1919, suggested that capillary dilatation occurred without increased blood flow. He termed this form of hyperemia "peristatic" and expressed the belief that it was due to arteriolar constriction and to paralysis of the capillary bed. This resultant increase in capillary diameter was followed by a decreased velocity of flow in the capillary bed and by consequent stasis. Nedzel[11] demonstrated that prolonged vasoconstriction was followed by prolonged vasodilatation after various forms

10. Ricker, G.: Die Entstehung der pathologisch-anatomischen befunde nach Hirnerschütterung in Abhängigkeit vom Gefässnervensystem des Hirnes, Virchows Arch. f. path. Anat. **226**:180-212, 1919.

11. Nedzel, A. S.: Vascular Spasm: Experimental Studies, Illinois Medical and Dental Monographs, vol. 3, nos. 3 and 4, 1943.

of stimulation. Lange and Boyd,[12] using fluorescein, found maximum capillary dilatation following the arteriolar constriction of freezing, with sequelae due to stasis and thrombosis of blood in the capillary bed. Scheinker [13] described vasodilatation following trauma, and Gilbert and de Takats [14] concluded that the stasis occurring about an area of cerebral infarction is an important cause of damage to the brain. Peterson [15] wrote of an acute spastic phase, which he called "ARS" (anabolism, reduction and spasm), and a chronic restorative phase, "COD" (catabolism, oxidation and dilatation). The latter is characterized by capillary vasodilatation, stasis and hypoxia.

We feel that we have established the existence of this phase of capillary dilatation in patients with peripheral arteriosclerosis, and, indeed,

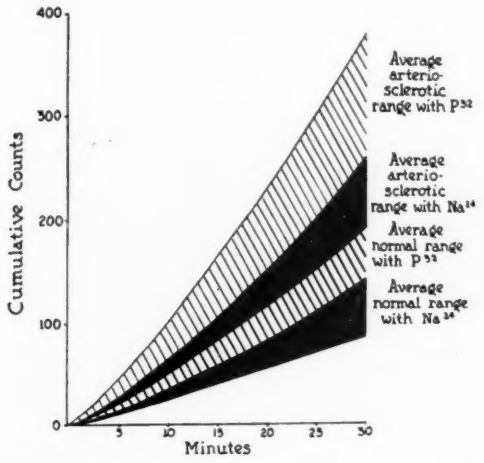

Fig. 5—Comparisons of results of tests made with radioactive phosphorus (P^{32}) and radioactive sodium (Na^{24}).

in all persons in whom arterial elasticity has diminished. Capillary stasis accounts for such typical stigmas in arteriosclerosis obliterans as rubor

12. Lange, K., and Boyd, L. J.: Functional Pathology of Experimental Frostbite and Prevention of Subsequent Gangrene, Surg., Gynec. & Obst. **80**:346-350 (April) 1945.

13. Scheinker, I. M.: Vasoparalysis of Central Nervous System, Characteristic Vascular Syndrome: Significance in Pathology of Central Nervous System, Arch. Neurol. & Psychiat. **52**:43-56 (July) 1944.

14. Gilbert, N. C., and de Takats, G.: Emergency Treatment of Apoplexy, J. A. M. A. **136**:659-665 (March 6) 1948.

15. Peterson, cited by Nedzel.[11]

of the dependent parts, pain at rest (hypoxia) and chronic changes in the skin and nails. It is interesting to note that the "build up" curve is steeper for patients in whom the symptoms of arteriosclerosis obliterans have increased in severity. The "build up" curve is flatter for patients in whom gangrene is about to appear and disappears for those in whom gangrene has ensued. The index, conversely, becomes lower for patients with increasing severity of the disease to the point of gangrene. In a further communication, the effect of therapeutic measures on the index will be discussed. It may be stated here that apparently vasospasm plays a minor role in arteriosclerosis. However, there is evidence that interruption of the pathways of the sympathetic nerve fibers will at times be effective. It may be postulated that in arteriosclerosis obliterans absence or diminution of the transmitted pulse, due to loss of elasticity in the blood vessels, results in loss of capillary tone and causes dilatation of the capillaries. We have evidence that, in the absence of extensive gangrene, the over-all rate of the blood

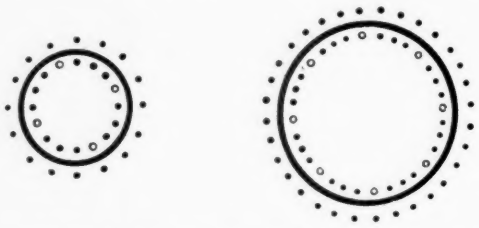

Fig. 6.—Comparison of large and small capillaries, indicating the greater surface available for diffusion (transfer of ions) when the concentration of ions within the capillary equals that outside the capillary. The black dots represent stable phosphate ions and the white dots radioactive phosphate ions; they appear in a ratio of about $10^{13}:1$.

flow is not appreciably slowed. When extensive gangrene is present little or no isotope is deposited in the extremity. This is due to obstruction of all major vessels in the extremity, and we feel that it is a late development in the disease process.

SUMMARY

Methods of determining the peripheral blood supply, with a consideration of the use of radioactive isotope tracers in this problem, are discussed.

The present study may be summarized as follows:

1. One hundred patients from the wards of the Cook County Hospital were each given an intravenous injection of 200 microcuries of P^{32}, and the "build-up" curves indicating deposition of the radioactive isotope

were determined. A semilogarithmic plotting of these curves resulted in what was essentially a straight line; the reciprocal of its slope was considered the index of circulation. These indexes fell into a normal distribution pattern, and the patients with arteriosclerosis and those over 50 years of age fell into well defined groups. The diffusion of P^{32} into the tissues was faster in older and in arteriosclerotic patients. Capillary dilatation is thought to be the chief cause of this phenomenon.

2. Observations of previous workers on capillary dilatation and stasis are discussed. The concept that stasis due to capillary dilatation, rather than vascular spasm, is responsible for the signs and symptoms of peripheral arteriosclerosis is presented.

3. Variations in the index will be presented in a subsequent communication,[16] and the diagnostic and prognostic significance of variations in the index will be discussed.

104 South Michigan Avenue.

16. Schaffner, F.; Friedell, M. T.; Pickett, W. J., and Hummon I. F. Jr.; Radioactive Isotopes in the Study of Peripheral Vascular Disease: II. Method of Evaluation of Various Forms of Treatment, Arch. Int. Med., to be published.

RADIOACTIVE ISOTOPES IN THE STUDY OF PERIPHERAL VASCULAR DISEASE

II. Method of Evaluation of Various Forms of Treatment

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WILLIAM J. PICKETT, M.D.
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IRVIN F. HUMMON Jr., M.D.
CHICAGO

EVALUATION of the peripheral circulation can be accomplished with the use of radioactive isotopes.[1] Determination of a circulatory index depends on the rate of deposition of radioactive phosphorus (P^{32} as a phosphate ion, in either phosphoric acid [H_3PO_4] or sodium phosphate [Na_2HPO_4]) in the tissues of an extremity; the index is then derived from a semilogarithmic plotting of the minute by minute increase in radioactivity in a selected site in the extremity (usually the sole of the foot). For statistical purposes, the reciprocal of the rate of deposition is used to calculate this index, according to the equations

$$\text{Index} = \frac{\log 20 - \log 2}{C_{20} - C_2} \quad \text{and}$$

$$\text{Index} = \frac{1}{C_{20} - C_2}$$

where C_{20} is the theoretic number of counts at the end of twenty minutes and C_2 is the theoretic number of counts at the end of two minutes.

In a series of normal persons, the mean rate of deposition of radioactive phosphorus in the tissues was actually less than in a group of patients with arteriosclerosis. Expressed by means of the index, which is a reciprocal function of the rate of deposition, the rate is higher for normal persons than for those with arteriosclerosis. The average index for the normal person is 0.160; for the person with arteriosclerosis

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1. Friedell, M. T.; Schaffner, F.; Pickett, W., and Hummon, I. F., Jr.: Radioactive Isotopes in the Study of Peripheral Vascular Disease: I. Derivation of a Circulatory Index, Arch. Int. Med., this issue, p. 608.

it is 0.089. This pronounced difference is explained on the basis of capillary dilatation, which provides a greater surface for diffusion of the phosphate ion. We believe that the capillary stasis resulting from this dilatation is a cause of many of the signs and symptoms of arteriosclerosis.

It was noted that the index for arteriosclerotic patients could be made to vary with treatment. The variations are to be considered from a prognostic and diagnostic standpoint.

MATERIAL AND METHODS

Clinical Material.—Twenty-six patients in the Cook County Hospital were studied. Table 1 demonstrates their distribution according to sex and age. Nine patients had diabetes, and 16 had ulcerating or gangrenous areas of the extremities. There was little difference between the age distribution of patients with diabetes and that of patients without the disease. Thirty-four series of determinations of indexes were made on these patients. In order to prevent an excessive accumulation of radioactive material in any patient, a repeated study always followed an interval of at least forty-eight hours.

TABLE 1.—*Distribution of Patients According to Sex and Age*

Sex	Patients with Diabetes	Patients Without Diabetes	Patients with Gangrene	Patients with Ulcers	Total Patients
Male	7	15	10*	6*	22
Female	2	2	0	1	4
Average age	66.8	65.1	63.1	69.9	65.7

* Four patients with gangrene and 2 with ulcers had diabetes.

Methods of Treatment.—Four methods of treatment were employed. These were (1) administration of histidine monohydrochloride and ascorbic acid, (2) lumbar sympathetic block with procaine hydrochloride, (3) administration of tetraethylammonium chloride and (4) lumbar sympathectomy. One or more methods of treatment were used on each patient. Tests with either tetraethylammonium chloride or lumbar block were given all candidates for sympathectomy to determine the probable efficacy of the operation.

Method of Procedure.—An index of circulation was determined for each patient, together with a clinical evaluation of the circulation at that time. Histidine monohydrochloride and ascorbic acid were administered in the dosage usually recommended [2]; the index was redetermined from ten to twenty days after the institution of treatment. For patients in whom lumbar sympathetic block was accomplished with procaine hydrochloride, determination of the circulatory index was begun about fifteen minutes later. When tetraethylammonium chloride was used, 500 mg. was slowly injected intravenously in a single test dose, and the subjective effects were noted by the patient; alterations in the blood pressure and the changes, if any, in the extremity were observed by the investigator; when

2. Friedell, M. T.; Drucker, E. F., and Pickett, W.: Histidine and Ascorbic Acid Treatment of Arteriosclerosis Obliterans (with Radioactive Isotope-Estimations of Circulatory Effects), J.A.M.A. **138**:1036-1039 (Dec. 4) 1948.

the blood pressure began to return to normal, the circulatory index was determined. Sympathectomy consisted of excision of the lower lumber ganglions of the side studied; the circulatory index was determined after the patient had recovered from the operation.

VARIATIONS IN THE CIRCULATORY INDEX AFTER TREATMENT

Patients with variations in the circulatory index after treatment were classified in four groups. In group 1 were patients whose circulatory index before treatment was in the range for arteriosclerosis and whose index shifted toward the normal range after treatment. In group 2 were patients whose circulatory index before treatment was in the range for arteriosclerosis and whose index after treatment deviated even farther from the normal range. In group 3 were those whose circulatory index before treatment was higher than the average range for persons with arteriosclerosis and whose index fell afer treatment into that range. In group 4 were patients whose circulatory index before treatment was above normal and whose index rose even higher after treatment; group 4 also included patients with a very low circulatory index who showed no response to treatment. (This failure to respond may be attributed to an inability of the capillaries to dilate or to failure of treatment, poorly performed lumbar block or lumbar sympathectomy, or defective medication.)

ANALYSIS OF TREATMENT AND SPECIFIC DETERMINATION OF GROUPING

Treatment with Histidine Monohydrochloride and Ascorbic Acid.—Ten patients were treated with histidine monohydrochloride and ascorbic acid; the results are shown in table 2. All the patients in group 1 showed good clinical results, and 2 patients in group 2 were clinically improved, but only 1 patient in group 3 responded to treatment. A typical case report of a patient who responded to treatment with histidine monohydrochloride and ascorbic acid and who was in group 1 is presented.

Case 1.—*History.*—J. L., a white man aged 57, was first seen by us in Cook County Hospital on Nov. 14, 1947. For a year previous to admittance, he had had intermittent pain in the calves of the legs after walking a distance of only about three blocks: the pain was relieved by rest. Recently the pain had become pronounced after walking but a few steps. Pain had been present at night in the right foot for one month prior to admission and had been progressively increasing in severity.

Physical Examination.—Examination revealed a well developed, fairly well nourished white man. The left arm had been amputated many years previously after trauma. There were no palpable arterial pulsations in either lower extremity. The skin of the legs and the toe nails showed moderate atrophy, and the skin of the dorsal surfaces of the right toes and foot was discolored, with a purplish

pallor. The oscillometric studies revealed an absence of pulsations in the lower extremities.

Course.—During the patient's stay in the hospital, papaverine and lumbar block with procaine hydrochloride had produced no relief from symptoms. Injection of 200 microcuries of radioactive phosphorus (P^{32}) revealed a circulatory index of 0.081. Histidine monohydrochloride and ascorbic acid were administered; forty-eight hours later the pain in the foot at night had diminished to the point where the patient could sleep without opiates, and he became ambulatory. The discoloration of the toes and foot gradually lessened, so that ten days after treatment was begun the cyanosis involved only the tips of the toes. Reevaluation with the use of P^{32} at that time indicated that the circulatory index was 0.104. The patient was discharged without further treament and was instructed to continue therapy with histidine monohydrochloride and ascorbic acid.

In this case the change in the circulatory index under treatment reveals that the histidine monohydrochloride and ascorbic acid had an

TABLE 2.—*Response by Groups to Various Forms of Treatment*

Treatment	Group	No. of Determinations	Results	
			Improvement	No Change
Histidine monohydrochloride and ascorbic acid..	1	3	3	0
	2	3	2	1
	3	4	1	3
	4	0	0	0
Sympathectomy	1	1	0	1
	2	3	2	1
	3	2	1	1
	4	1	0	1
Tetraethylammonium chloride	1	5	4	1
	2	3	2	1
	3	1	0	1
	4	1	0	1
Lumbar sympathetic block	1	4	3	1
	2	2	2	0
	3	0	0	0
	4	1	0	1

effect on the peripheral circulation. The return of the circulatory index toward the normal range caused this patient to be classified in group 1, and the good clinical response was consistent with the prognosis of the group.

The preliminary circulatory index in another patient was 0.058. After intravenous injection of 500 mg. of tetraethylammonium chloride, the circulatory index rose to 0.128. A course of treatment with histidine monohydrochloride and ascorbic acid was given next; the subsequent circulatory index was 0.093. A similar response was thus indicated to two different kinds of vasodilating mechanisms. The patient also showed clinical improvement after each form of treatment.

Treatment by Lumbar Sympathetic Block with Procaine Hydrochloride.—Determination of the circulatory index for 7 patients was made before and after lumbar block. Six patients were in groups 1

and 2 (table 2), and 1 was in group 4 (a subsequent trial with tetraethylammonium chloride did not alter the index, and the patient remained classified in group 4). One patient in group 2 had a preliminary circulatory index of 0.105. After lumbar block the index fell to 0.051 and after lumbar sympathectomy to 0.079. The grouping was thus constant. The patient showed a good clinical result.

Treatment with Tetraethylammonium Chloride.—Ten patients, some of whom had received other forms of treatment, were treated with tetraethylammonium chloride; table 3 shows comparative results. Again, in the limited series studied, there is excellent agreement of circulatory indexes and groupings, as determined by response to two different methods of treatment. This series of determinations resulted in the classification of 4 patients in group 1; 2 showed clinical improvement. One patient was in group 3, and 2 were in group 4. None of these evinced any significant clinical response (table 2).

Treatment by Lumbar Sympathectomy.—The indications for lumbar sympathectomy in the treatment of arteriosclerosis obliterans have been indefinite. Lumbar ganglionectomy is the procedure of choice and was the method employed in these cases. The age of the patient and the surgical risk, as well as the doubtful benefits, have militated against widespread application of this procedure. Some investigators have reported considerable success, with a very low surgical risk. Of the 7 patients treated with lumbar ganglionectomy, 1 was in group 1, 3 were in group 2 and 2 in group 4. A review of preliminary studies of circulatory indexes on these patients revealed little difference in the groupings obtained by other means. Table 3 shows the variations in results when repeated series of estimations of circulatory indexes were made with various types of treatment. The successful results of sympathectomy are illustrated in the following cases.

Case 2.—*History.*—A. M., a white man aged 61, was first seen by us at the Cook County Hospital on April 27, 1948. His right leg had been amputated in 1947 because of gangrene. The toes of the left foot had been amputated during the two years previous to admission.

Physical Examination.—On this admission, a painful ulcer was present at the site of the amputated toes. There was no evidence of peripheral pulsation in the remaining parts of the extremity. A circulatory index of 0.105 was obtained.

Course.—A paravertebral lumbar sympathetic block was performed on the left side; subsequently, the circulatory index fell to 0.051. There was clinical improvement. Lumbar ganglionectomy was performed on the left side, and eight days after operation the circulatory index was 0.079. The patient noted subjective improvement, and the ulcer began to heal.

Case 3.—*Physical Examination.*—E. E., a white man aged 57, was first seen by us on Feb. 28, 1948. The first, second, third and fifth toes of the left foot were gangrenous. No peripheral pulsations were noted. There was no evidence of

diabetes. Amputation of the right leg at midthigh had been performed in 1944 because of a nonunited fracture of the femur. Determination of the circulatory index revealed an index of 0.057 (within the range indicating arteriosclerosis).

Course.—Because of the evidence of rapid deposition of radioactive phosphorus in the foot, it was felt that local amputation would be sufficient. On March 6, amputation of the toes was performed. The sites of amputation became painful, infected and indolent. The intravenous injection of 500 mg. of tetraethylammonium chloride on March 18 relieved the pain. Determination of the circulatory index showed that it had risen to 0.117; the classification was thus group 1. On March 25, left lumbar sympathectomy (ganglionectomy) was performed. The immediate clinical results were good. By April 1, the ulcer sites were clean and healing well. A repetition of studies with radioactive phosphorus showed a circulatory index

TABLE 3.—*Classification of 7 Patients with Regard to Indexes and Groups After Two or More Forms of Treatment*

	Indexes					
Patient	Before Treatment	After Lumbar Sympathetic Block	After Tetraethylammonium Chloride	After Histidine, Monohydrochloride and Ascorbic Acid	After Sympathectomy	Comment
A	0.051	0.333 (4)*	0.051 (0)	.....	.....	Poor response to block, no response to tetraethylammonium chloride
B	0.057	.....	0.117 (1)	.....	0.029 (2)	Good response to both procedures
C	0.058	.....	0.128 (1)	0.093 (1)	.....	Good response to both procedures
D	0.090	0.078 (2)	0.080 (2)	.....	.....	Good response to both procedures
E	0.105	0.051 (2)	.....	.....	0.079 (2)	Good response to both procedures
F	0.137	0.187 (3)	.....	.....	0.044 (3)	Poor response to sympathectomy
G	0.170	.....	.....	.....	0.306 (4) 0.060 (3)	Change after rest in bed for one month after operation

* Numbers in parentheses indicate groups.

of 0.029. The patient's classification was now group 2. The patient continued to improve and was discharged without further treatment.

Failures of sympathectomy are particularly distressing. On a few occasions it seemed to us that sympathectomy precipitated a previously impending gangrene.

CASE 4.—*History and Physical Examination.*—K. O., a white man aged 57, was admitted to the Cook County Hospital on Feb. 18, 1948, with severe pain and swelling of the right foot. He was known to have had diabetes for the past twelve years. While in the hospital, he suffered from severe pain at night and from claudication and paresthesia. There was no peripheral pulsation in the right lower extremity. The circulatory index determined on the right leg on February 24 was 0.327.

Course.—On February 27 the circulatory index for the left leg was 0.056. On March 1, 500 mg. of tetraethylammonium chloride was administered intravenously; clinical improvement in the left leg and bilateral relief of pain resulted. At that

time the circulatory index for the right leg was raised to 1.000, which classified the patient in group 4. On March 8, 9, 10 and 11, bilateral lumbar paravertebral sympathetic blocks were performed, without obvious relief. On March 23, a left lumbar sympathectomy was performed. On March 26, the right leg was gangrenous, and a supracondylar amputation was necessary. On March 29, the left foot became discolored and cyanotic. The circulatory index was redetermined; it was 0.070. However, there was little clinical improvement. Signs of impending gangrene developed in the left foot, and the circulatory index for the left leg rose to 0.300, again establishing classification in group 4. The patient refused amputation. When he was last examined, the gangrenous process was extending.

COMMENT

The four types of treatment used in connection with this study are all directed at vasodilatation, which is a complex physiologic mechanism. Herrick, Essex and Blades [3] demonstrated that lumbar sympathectomy in dogs increased the blood flow in the femoral artery. Tetraethylammonium chloride, though its action is systemic, and certainly lumbar block may be considered to do the same.[4] The effect of therapy with histidine monohydrochloride and ascorbic acid has been likened to a histamine effect.[5] The effect of histamine on capillary diameter is variable, and its transitory effects on other vessels have been difficult to establish. Best and Taylor [6] asserted that there is an independent circulation of the capillaries. According to these authors, one of the greatest regulators of capillary diameter is the oxygen content of the capillary blood. Oxygenation readily causes capillary constriction. Histamine may affect both arteriolar and capillary diameter. It is possible that the independent circulation of the capillaries is dependent mainly on the need for oxygen in the local tissues, and that all other vasomotor mechanisms, including histamine, are of secondary importance. The thesis of independent circulation of the capillaries is borne out by some of the observations we have made.

In a previous paper [1] we pointed out that the rate of diffusion of I^{132} into the tissues of young persons is lower than that in persons over 50 years of age. In arteriosclerotic extremities the rate of diffusion

3. Herrick, J. F.; Essex, H. E., and Baldes, F. J.: Effect of Lumbar Sympathectomy on Blood Flow in Femoral Artery of Dog, Am. J. Physiol. **101**: 213-217, 1932.

4. Berry, R. M.; Campbell, K. N.; Lyons, R. H.; Moe, G. K., and Sutler, M. R.: Use of Tetraethylammonium in Peripheral Vascular Disease and Causalgic States: New Method for Producing Blockade of Autonomic Ganglia, Surgery **20**:525-535, 1946.

5. Wirtschafter, Z. T., and Widmann, R.: Elaboration of Histamine in Vivo in the Treatment of Peripheral Vascular Disorders, J.A.M.A. **133**:604-605 (March 1) 1947.

6. Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, ed. 3, Baltimore, Williams & Wilkins Company, 1943, p. 443.

is distinctly more rapid than in the normal extremities. Therefore, we believe that the total capillary bed is greater in capacity in patients with arteriosclerosis than in normal persons. Only when arteriosclerosis has advanced to a pronounced degree does the circulatory index advance above normal. This increase indicates a considerable decrease in the diffusion of P^{32} and signifies an obstruction or disappearance of the capillary bed.

Figure 1 illustrates this concept of the relation of the size of the normal capillary to that of the normal artery. As the arteries become sclerosed and inelastic but remain patent, the capillaries dilate. This permits more rapid diffusion of P^{32} into the tissues, and a lower circulatory index results. Finally, as the process advances, the arteries

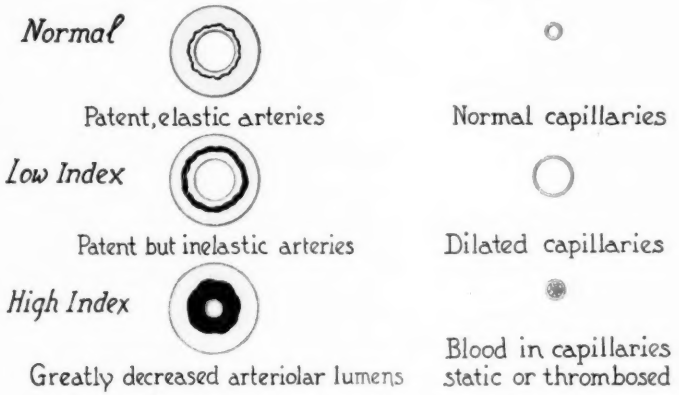

Fig. 1.—Variations in the circulatory index for patients with arteriosclerosis depend on the relative diameter of the arteries and capillaries except when the flow of blood is greatly diminished.

become occluded and the capillaries cease to function. It is possible that "sludging" (Knisely, Eliot and Bloch[7]) and thrombosis of the capillaries occur at this point. If one accepts this theory, there is little difficulty in establishing a realistic view of the relation of the arteriosclerotic state to the rate of appearance of the radioactive phosphorus in the tissues of the leg.

In the patients in group 1, the circulatory index was at first low, whereas after the application of a vasodilating mechanism the circula-

7. Knisely, M. H.; Eliot, T. S., and Bloch, E. H.: Sludged Blood in Traumatic Shock: Microscopic Observations of Precipitation and Agglutination of Blood Flowing Through Vessels in Crushed Tissues, Arch. Surg. **51**:220-236 (Nov.-Dec.) 1945.

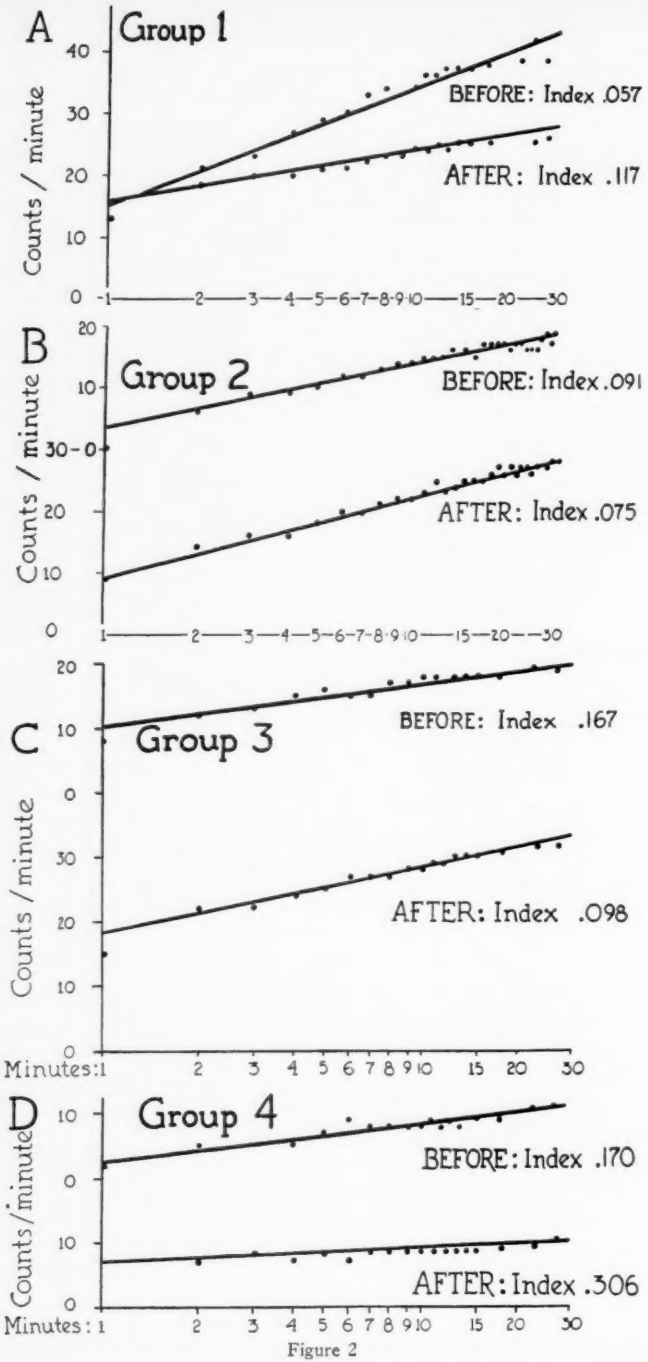
A
Group 1
BEFORE: Index .057
AFTER: Index .117
Counts / minute
B
Group 2
BEFORE: Index .091
AFTER: Index .075
Counts / minute
C
Group 3
BEFORE: Index .167
AFTER: Index .098
Counts / minute
Minutes: 1 2 3 4 5 6 7 8 9 10 15 20 30
D
Group 4
BEFORE: Index .170
AFTER: Index .306
Counts / minute
Minutes: 1 2 3 4 5 6 7 8 9 10 15 20 30

Figure 2

tory index returned toward normal and clinical improvement was noted (fig. 2 *A*). Such grouping was noted in thirteen series of determinations, and clinical improvement (an increase in blood flow to the extremity, a lowering of the oxygen deficit, and resulting restoration of capillary tone) was also noted in ten instances (table 4).

In eleven series of determinations, the alterations of circulatory indexes resulted in classification of the patients in group 2 (table 4). Improvement was noted in eight of eleven clinical trials. Patients in group 2 had a circulatory index below normal which fell even lower on vasodilatation. This drop was interpreted as an indication of the presence of minor vasospastic elements, accompanied with an improvement in circulation after treatment (fig. 2 *B*). However, capillary tone was not restored, and the rate of diffusion of P^{32} increased, indicating additional capillary dilatation.

TABLE 4.—*Immediate Results and Average Indexes for Patients in Each Group Before and After Treatment*

Group	Number of Patients	Index		Results	
		Before	After	Improvement	No Change
1	13	.087	.120	10	3
2	11	.083	.062	8	3
3	7	.140	.072	2	5
4	3	.186	.500+	0	3

In the patients of group 3 the circulatory index was originally high and fell after vasodilatation, thus indicating the presence of a major vasospastic element, the release of which restored blood flow to the dilated capillaries (fig. 2 *C*). Improvement was noted only twice in the seven clinical trials.

The data on group 4 indicate a further deterioration in the capacity of the circulation to respond to treatment. Attempts at vasodilation further decreased the rate of capillary diffusion of P^{32} (fig. 2 *D*). There is evidence that attempts at temporary vasodilation are futile and that sympathectomy may be dangerous when the patient is in such a state. It is possible that vasodilation permanently injuries the capillary bed and that it may have hastened the development of thrombosis and the

Fig. 2.—Variations in response to treatment: *A* (group 1), circulatory index originally low, then returned to normal; capillary tone restored. *B* (group 2), index low and became lower; increased flow of blood, caused by removal of minor vasospastic elements, further dilated the already enlarged capillaries. *C* (group 3), index high and became lower; predominant vasospastic element relieved; flow of blood to dilated capillaries increased. *D* (group 4), index high and remained constant or became higher; flow of blood permanently diminished; amputation necessary.

extension of gangrene in the patients of this group. None of the patients in this group responded to treatment; all underwent amputation.

No attempt was made to study the mechanism of capillary thrombosis. That it can occur has been shown by Lange and Boyd[8] in their work on frostbite, and by Knisely and his associates[7] in their work on sludging. It is possible that the stasis resulting from capillary dilation may lead to anoxia, sludging and subsequent thrombosis. It must be emphasized that our conclusions represent a series of inferences based on our observations. We believe that the explanations put forth are the simplest to fit the known facts. There is as yet no adequate means of visualizing in the human subject the effects of the arteriosclerotic process on the arteries and the arterioles. We feel that until such time as a simple, practical form of capillary microscopy is available for general use the most accurate determination of the status of the vascular bed and its pathologic response can be made with the use of radioactive isotopes. The increasing availability of the isotopes and of simple measuring machines at relatively low cost should be further exploited in the diagnosis of, and the evaluation of treatment in, peripheral vascular disease.

SUMMARY AND CONCLUSIONS

The derivation of an index of circulation, calculated from the rate of diffusion of intravenously injected radioactive phosphorus into the tissues of the lower extremity, is reviewed.

The effect of treatment on this index of circulation was determined. Four forms of treatment were used: administration of histidine monohydrochloride and ascorbic acid, lumbar sympathetic block with procaine hydrochloride, administration of test doses of 500 mg. of tetraethylammonium chloride and lumbar sympathectomy.

Thirty-four series of determinations were made on 26 patients. Patients were classified into four groups: group 1, patients for whom the circulatory index was originally low and then rose toward normal; group 2, patients for whom the circulatory index was originally low and later fell; group 3, patients for whom the circulatory index was apparently originally normal and later fell, and group 4, patients for whom the circulatory index was originally above normal and then rose even higher.

The variations in the circulatory indexes were interpreted as signifying the response of the capillary bed to peripheral vasodilators. The capillaries are considered to have an independent circulation, based

8. Lange, K., and Boyd, L. J.: Functional Pathology of Experimental Frostbite and Prevention of Subsequent Gangrene, Surg., Gynec. & Obst. **80**:346-350, 1945.

largely on the demand for and deficit of oxygen. The responses to treatment in the patients in the four groups were as follows: In group 1, the capillary tone was restored; in group 2, minor vasospastic elements were relieved but capillary dilation persisted; in group 3, major vasospastic elements were relieved but capillary dilation persisted or increased, and in group 4, deterioration of peripheral circulation was almost complete and amputation was required.

The prognosis in groups 1 and 2 was favorable and in groups 3 and 4 unfavorable.

Radioactive phosphorus is useful as a diagnostic and prognostic tool in the evaluation of peripheral vascular states, such as arteriosclerosis obliterans.

CLINICAL STUDIES ON DICUMAROL® HYPOPROTHROMBINEMIA AND VITAMIN K PREPARATIONS

I. Superiority of Vitamin K_1 Oxide Over Menadione Sodium Bisulfite U.S.P. and Synkayvite® in Reversing Dicumarol Hypoprothrombinemia

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THE HYPOPROTHROMBINEMIA induced with dicumarol® (3, 3'-methylene-bis-[4-hydroxycoumarin]) is much more difficult to control than that which is the result of obstructive jaundice and other states characterized by deficient intake or absorption of vitamin K. Substances which have vitamin K activity in amount sufficient to reverse the hypoprothrombinemia of the latter states are wholly inadequate against the effect of dicumarol.® This report describes observations on the effect of three different compounds with vitamin K activity on the hypoprothrombinemia of human beings after dicumarol® therapy. Determination of the rapidity and degree to which the hypoprothrombinemia induced with this agent can be reversed is a logical and safe method of investigating the efficacy of these agents in man and is the basis on which these studies have been made.

There is general agreement that when bleeding occurs as the result of dicumarol® poisoning the main cause is prothrombin deficiency.[1] Other, less important, factors are at work as well. The role of previous trauma in determining the site of hemorrhage[2]; the fact that the prothrombin concentrations of persons who bleed may be higher than the concentrations of persons who do not; the fibrinogen concentration as influenced by dicumarol;®[3] and the role of arteriolar, capillary and

From the Department of Medicine, Emory University School of Medicine, and the Medical Service, Grady Hospital.

1. Roderick, L. M.: A Problem in the Coagulation of the Blood, Am. J. Physiol. **96**:413 (Feb.) 1931.

2. Barker, N. W.; Cromer, H. E.; Hurn, M., and Waugh, J. M.: The Use of "Dicumarol" in the Prevention of Postoperative Thrombosis and Embolism with Special Reference to Dosage and Safe Administration, Surgery **17**:207 (Feb.) 1945.

3. Irish, U. D., and Jaques, L. B.: The Effect of "Dicumarol" upon Plasma Fibrinogen, Am. J. Physiol. **143**:101 (Jan.) 1945.

venular dilatation in hemorrhage due to dicumarol®[4] all are factors of possible significance in bleeding consequent to administration of dicumarol.® This study is not concerned with these factors.

METHOD

One hundred and one patients in the medical wards at the Grady Hospital were given dicumarol® in daily oral doses, 300 mg. the first day and 200 mg. on each successive day, until the prothrombin time exceeded that of normal control plasma diluted to a concentration of 20 per cent with 0.85 per cent solution of sodium chloride. The patient either was then allowed to recover, untreated, to his normal prothrombin level or was given large single doses of menadione sodium bisulfite U. S. P. (hykinone®), synkayvite® (tetrasodium salt of 2-methyl-1,4-naphthohydroquinone diphosphoric acid ester) or vitamin K_1 oxide[5] (oxide of 2-methyl-3-phytyl-1,4-naphthoquinone). None of the patients in this group had gross renal or hepatic dysfunction, a tendency to bleed or a history of recent bleeding. All initially had a prothrombin time within two seconds of that of undiluted normal control plasma. After administration of the agent to be tested, samples of blood were withdrawn at intervals of 2, 4, 6, 8, 10, 12, 18 and 24 hours on the first day and daily thereafter until the prothrombin time was normal. Reversal of the patient's prothrombin time to, and its maintenance at or above, that for 30 per cent normal plasma were regarded as satisfactory evidence of protection of that patient against the possibility of hemorrhage due to dicumarol.[6]

Vitamin K_1 oxide, menadione sodium bisulfite U. S. P. and synkayvite® were chosen as test materials because they had all been given in large single doses intravenously without toxic effects, both in this clinic and elsewhere. The largest dose of menadione sodium bisulfite U.S.P. customarily given in a single intravenous injection is 60 to 75 mg.[6] Accordingly, the effect of 64 mg. was first observed and later the dose was increased twofold and threefold. Synkayvite® in 500 mg. doses had been used in this clinic, and vitamin K_1 oxide had been given in amounts up to 2,000 mg. here and elsewhere,[7] without toxic effects, and these doses were used in this study. Undiluted menadione sodium bisulfite U. S. P. and

4. (*a*) Bingham, J. B.; Meyer, O. O., and Pohle, F. J.: Studies on the Hemorrhagic Agent 3, 3′-Methylenebis (4-Hydroxycoumarin): I. Its Effect on Prothrombin and Coagulation Time of Blood of Dogs and Humans, Am. J. M. Sc. **202**:563 (Oct.) 1941. (*b*) Shlevin, E. L., and Lederer, M.: Uncontrollable Hemorrhage After "Dicoumarol" Therapy with Autopsy Findings, Ann. Int. Med. **21**:332 (Aug.) 1944.

5. The vitamin K_1 oxide was furnished by the Medical Division, Merck and Co. Inc.

6. (*a*) Barker, N. W.; Hines, E. A.; Kvale, W. F., and Allen, E. V.: Dicumarol, Its Action, Clinical Use and Effectiveness as an Anticoagulant Drug, Am. J. Med. **3**:634 (Nov.) 1947. (*b*) Combined Staff Clinics: "Thromboembolism," ibid. **3**:753 (Dec.) 1947. (*c*) Evans, J. A., and Dee, J. F.: Anticoagulant Treatment of Postoperative Venous Thrombosis and Pulmonary Embolism, New England J. Med. **238**:1 (Jan. 1) 1948.

7. Davidson, C. S.; Freed, J. H., and MacDonald, H.: The Effect of Vitamin K_1 Oxide upon the Anticoagulant Properties of Dicumarol, Am. J. M. Sc. **210**:634 (Nov.) 1945.

synkayvite® were given intravenously over a three to five minute period. When vitamin K_1 oxide, a heavy oil, was given intramuscularly, the desired dose was taken up in a syringe and administered through an 18 gage needle. Vitamin K_1 oxide was prepared for intravenous administration according to the method outlined by Davidson and MacDonald.[8]

Determinations of prothrombin time were made daily. With a few exceptions, which occurred early in the study, all the samples of plasma withdrawn during any given day were tested at the same time. All blood was refrigerated at 4 C. until immediately before testing. The prothrombin time determinations were made by the method of Quick. The thromboplastin was from rabbit brain obtained from a commercial source (Difco Laboratories, Inc.). Each day's supply was made up on the day on which it was used. To a glass test tube containing 0.1 cc. of the thromboplastin solution and 0.1 cc. of the plasma sample at 37 C., 0.1 cc. of 0.025 molar solution of calcium chloride was added rapidly. This mixture was agitated in the water bath for several seconds, removed and tilted at intervals of somewhat less than a second, the appearance of a clot being timed with a stopwatch. Normal control plasmas were tested in the undiluted state and after dilution with 0.85 per cent sodium chloride solution to concentrations of 30, 20 and 10 per cent.

RESULTS

Time from Beginning of Treatment with Dicumarol® Until Significant Hypoprothrombinemia Was Obtained.—Figure 1 shows the days required for dicumarol® to lengthen the prothrombin time of 101 patients to longer than that of 20 per cent normal plasma. For 82 patients this effect was achieved in from 2 to 4 days (total dose of dicumarol,® 500 to 900 mg.); however, 17 patients required from 5 to 10 days (1.1 to 2.1 Gm. of dicumarol®). The fact that approximately 1 patient 5 took more than 4 days to attain what may be regarded as a therapeutically satisfactory diminution in prothrombin concentration is worthy of emphasis. This variability of response did not appear to be closely related to age, sex, race, body size or physical state. The largest subject, a man weighing over 250 pounds (113.4 Kg.), required 6 days' treatment before his prothrombin time exceeded that of 20 per cent normal plasma. The 3 smallest patients, each weighing between 80 and 100 pounds (36.3 and 45.4 Kg.), required 2, 5 and 8 days, respectively.

Of 7 teen age patients studied, 1 required medication for 5 days; 2, for 4 days, and 4, for 3 days (an average of 3.6 days) before the desired prothrombin level was attained. Twelve patients were over 60 years of age. The time needed to decrease their prothrombin activity averaged 3.2 days.

Predictability of Response to Dicumarol.®—Our data suggest that, on the basis of the amount of dicumarol® needed by a given patient, one may in the near future predict how much may be necessary during

8. Davidson, C. S., and MacDonald, H.: The Effect of Vitamin K_1 Oxide on Hypoprothrombinemia Induced by Dicoumarol, New England J. Med. **229**:353 (Aug. 26) 1943.

a second course. Five patients who were allowed to recover, untreated, from the effect of dicumarol® were treated a second time, after a period of at least 2 days, during which the prothrombin time was equal to that of normal plasma. Their original requirements varied from two to eight daily doses. During the second course of dicumarol® medication their requirements varied from the first course by no more than two doses. This observation was also made on 8 patients who had received menadione sodium bisulfite intravenously. Again, those who had required much or little dicumarol® the first time needed a similar amount the second time, and none of the courses varied by more than 2 days.

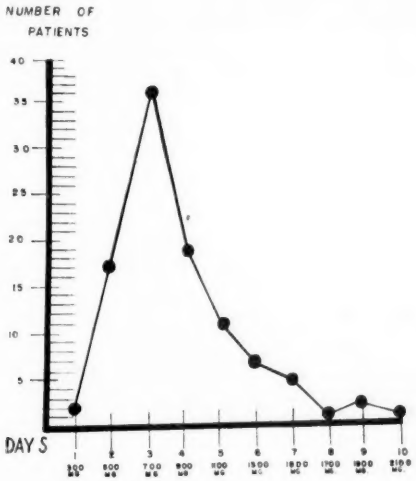

Fig. 1.—Dicumarol® required to prolong prothrombin time to beyond that of a 20 per cent normal plasma—initial course; 101 cases.

Effectiveness of Vitamin K_1 Oxide, Menadione Sodium Bisulfite U.S.P. and Synkayvite® in Completely Reversing the Effect of Dicumarol.®—The time required for recovery from the effect of dicumarol® was investigated in various circumstances for 80 patients.

Controls: As a control group, 19 persons were allowed to recover without treatment. It was found that an average of 5.7 days elapsed before the patients' prothrombin time arrived at, or was shorter than, that of 30 per cent normal plasma. The shortest period that elapsed until this return was 2 days (2 patients); the longest, 12 days (1 patient). About half the patients (9) required 6 or 7 days before their prothrombin times were shorter than that of 30 per cent normal plasma.

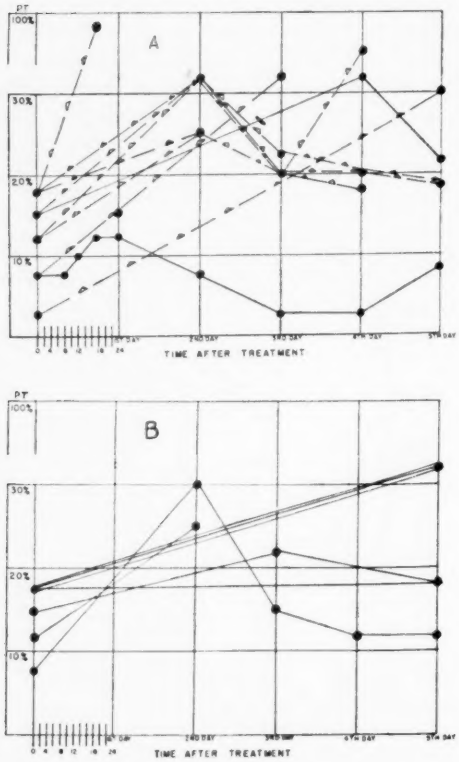

Fig. 2.—Effect of intravenous administration of menadione sodium bisulfite U. S. P. on hypoprothombinemia induced by ingestion of dicumarol.® In *A*, unbroken lines indicate values for a 64 mg. dose; the broken line with triangles indicates values for doses of 100 or 120 mg. In *B*, the dose was 180 mg. Determinations of prothrombin time (*PT*) were made on plasma taken at intervals of 2, 4, 6, 8, 10, 12 and 18 hours after the menadione sodium bisulfite was administered, and then given daily thereafter. The prothrombin times are compared with the average of those for 3 normal subjects (undiluted plasmas, as well as plasmas diluted to 30, 20 and 10 per cent, as shown in the vertical column). Each line indicates the course of one patient. The only points plotted are those which show change in prothrombin concentration from one area of the figure to another. When the prothrombin time remained shorter than that of 30 per cent normal plasma, no more points were plotted. Otherwise, the course of the changes in prothrombin time was plotted for 5 days after treatment whenever possible.

Menadione Sodium Bisulfite U. S. P.: Nineteen patients with the dicumarol® effect, as described, were given menadione sodium bisulfite U. S. P. in single intravenous doses of 64 to 180 mg. An average of 4.7 days elapsed before the prothrombin times were shorter than that of 30 per cent normal plasma. The first 4 observations were made on the effect of doses of 64 mg., but the lack of response to this amount led to the use of larger quantities, 8 patients receiving 120 mg. and 7 patients, 180 mg. The largest doses had no more effect than the smaller ones. An average of more than 7 days elapsed after treatment with 180 mg. of menadione sodium bisulfite before the prothrombin times were shorter than that for 30 per cent normal plasma, whereas the average for the patients given 120 mg. was 3.5 days, and that for the group given 64 mg., about 4 days.

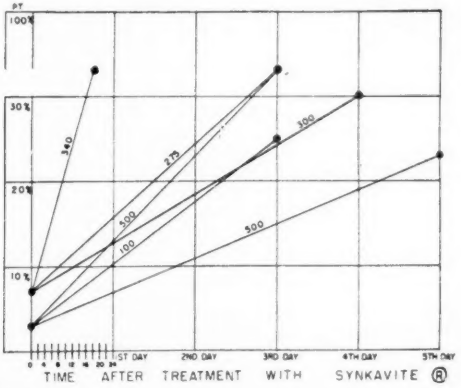

Fig. 3.—Effect of administration of synkayvite® on hypoprothrombinemia (prothrombin time-*PT*) induced with ingestion of dicumarol.® The doses are indicated in milligrams on the lines. Method of charting is the same as described for figure 2.

One patient given 120 mg. of menadione sodium bisulfite responded with a shortening of her prothrombin time to less than that of 30 per cent normal plasma in 18 hours. Five of this group of 19 patients showed temporary response to menadione sodium bisulfite, which occurred 24 to 48 hours after the injection. For 4 of these patients, the prothrombin time became equal to, or slightly shorter than, that of 30 per cent normal plasma, but after this temporary improvement the prothrombin times again lengthened and the subsequent recovery of these patients from the dicumarol® effect did not appear to have been affected by administration of menadione sodium bisulfite. Figure 2 shows the course for 16 patients who received this drug.

Synkayvite®: Six patients were given synkayvite® intravenously, in single doses of from 100 to 500 mg. The prothrombin time of one patient given 340 mg. reached a level between that of 30 per cent normal plasma and that of undiluted normal plasma at the end of 18 hours. The remaining patients showed minimal responses, the average time required after injection of synkayvite® for the prothrombin time to return to shorter than 30 per cent normal being 5.3 days (including the patient aforementioned). The 3 patients given 500 mg. of this drug showed no better response than those to whom smaller doses were administered. Figure 3 shows the course of the patients in this group.

Vitamin K_1 Oxide: Vitamin K_1 oxide administered intravenously in doses of 500 to 2,000 mg. was strikingly superior to the other sub-

TABLE 1.—*Effect of Treatment on Prolonged Prothrombin Time Showing Average Number of Days Required for Dicumarol®-Lengthened Prothrombin Time to Return to Shorter than That of 30 Per Cent Normal Control Plasma*

Number of Patients	Treatment	Time (Days)
19	None (control)	5.7
19	Menadione sodium bisulfite U. S. P. (64-180 mg., intravenously)	4.7
6	"Synkayvite" (100-500 mg., intravenously)	5.3
5	Vitamin K_1 oxide (500 mg., intramuscularly)	4.4
5	Vitamin K_1 oxide (100-250 mg., intravenously)	2.5
6	Vitamin K_1 oxide (500 mg., intravenously)	0.4
20	Vitamin K_1 oxide (800-2,000 mg., intravenously)	0.6

stances tested. The therapeutic goal was attained in approximately one-tenth the time required for synkayvite,® menadione sodium bisulfite or the normal controls. Of the 26 patients who received from 500 to 2,000 mg. of vitamin K_1 oxide intravenously, only 1 required more than 1 day for return to a prothrombin level equivalent to, or shorter than that of 30 per cent normal plasma. He was given 1,000 mg. of the preparation. This man, aged 45, with chronic addiction to alcohol, had been admitted with delirium tremens 10 days before the first dose of dicumarol.® He had required four daily doses (900 mg.), an average amount, to prolong his prothrombin time beyond that of 20 per cent normal plasma. Results of his hepatic function tests (sulfobromophthalein sodium excretion, total protein, formaldehyde-gel reaction, icterus index, thymol turbidity, cephalin flocculation and prothrombin time) were all within normal limits.

Vitamin K_1 oxide was administered intramuscularly in single 500 mg. doses to 6 patients. Its effect was without significance, and the course of these patients following this medication could not be distinguished from that of the untreated controls. Vitamin K_1 oxide was

given to 5 patients in single intravenous doses of 100 to 250 mg. The time which elapsed before the average prothrombin time became less than that of 30 per cent normal plasma was 2.5 days, a period definitely shorter than that for the control group and for the groups treated with menadione sodium bisulfite and synkayvite,® given intravenously, and with vitamin K_1 oxide, given intramuscularly. This time was significantly longer, however, than that which elapsed after the intravenous administration of vitamin K_1 oxide in amounts of 500 mg. or more. The results of this study are summarized in table 1.

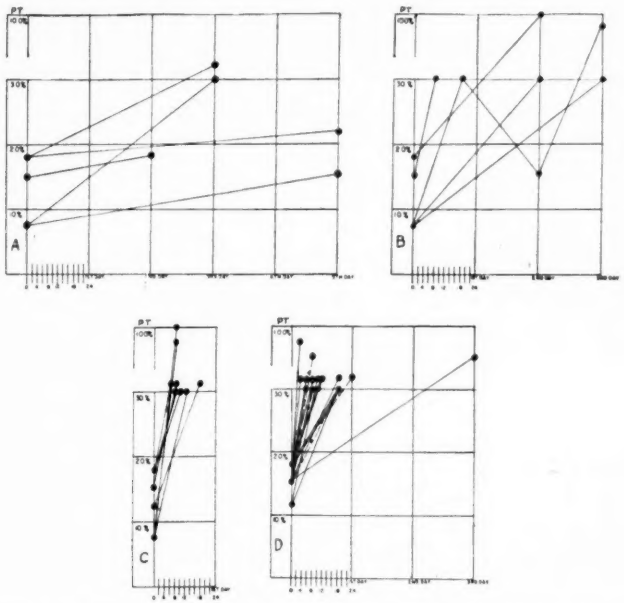

Fig. 4.—Effect of administration of vitamin K_1 oxide on hypoprothrombinemia induced with ingestion of dicumarol.® Method of charting is the same as that described for figure 2. *A*, time after treatment with 500 mg. of vitamin K_1 oxide given intramuscularly; *B*, time after treatment with 100 to 250 mg. of vitamin K_1 oxide given intravenously; *C*, time after treatment with 500 to 750 mg. of vitamin K_1 oxide given intravenously, and *D*, time after treatment with 1,000 mg. (solid line) and 2,000 mg. (broken line with triangles) of vitamin K_1 oxide given intravenously.

Figure 4 illustrates the effect on the prothrombin time of the various doses of vitamin K_1 oxide used. In the group of patients studied by us, the 500 mg. dose seemed as effective as larger amounts. The superiority of the intravenous over the intramuscular route is obvious.

Time Required to Raise the Prothrombin Time Above the Level for 10 per Cent Normal Plasma.—No attempt was made to prolong the prothrombin time for these patients beyond that of 10 per cent normal plasma. However, during the course of this study, estimations of the prothrombin time on plasmas withdrawn immediately prior to treatment showed that the prothrombin times of 16 patients were longer than that of 10 per cent normal plasma. No selection of the type of treatment which was given these patients was possible, as the determinations of prothrombin time were not made until after the treatment had been given. However, the 16 instances were scattered in such a way as to enable some comparison, and it was possible to estimate the time which elapsed after treatment until the prothrombin time became shorter than that of 10 per cent normal plasma. Knowledge of the effect of the vitamin K preparations on hypoprothrombinemia of this severity is especially desirable, because it is at such levels that severe bleeding is likely to occur. Also, as will be mentioned later, other workers have selected this area for testing the efficacy of menadione sodium bisulfite. These observations are summarized in table 2. Four of these patients received menadione sodium bisulfite intravenously. An average of 37 hours elapsed before the prothrombin time was shorter than that of 10 per cent normal plasma. This average was disproportionately prolonged by 1 patient (fig. 5) whose prothrombin time, after an evanescent shortening, remained prolonged for 5 days, and it was felt necessary to administer vitamin K_1 oxide. When data on this patient are excluded, the average time required to shorten the prothrombin time of the other 3 patients to less than that of 10 per cent normal plasma was 9 hours.

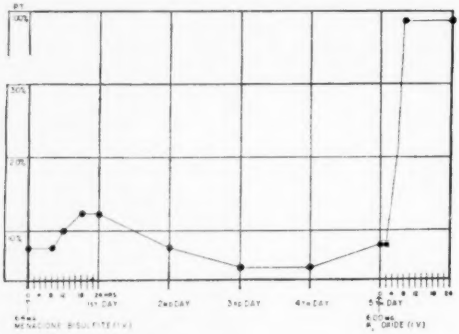

Fig. 5.—Effect of single intravenous doses of menadione sodium bisulfite (64 mg.) and vitamin K_1 oxide (600 mg.) on the prothrombin time (*PT*) of a patient previously given dicumarol.®

Six patients of this group received synkayvite.® An average time of 14 hours elapsed before their prothrombin times shortened to less than that of 10 per cent normal plasma, the shortest time being 10 hours (2 patients) and the longest, 18 hours (3 patients).

When subjected to this method of analysis, vitamin K_1 oxide was again shown to be greatly superior to the other substances tested. Of the 6 patients given this agent intravenously (2 received but 100 mg.

TABLE 2.—*Time (Hours) Required by Menadione Sodium Bisulfite U. S. P., Synkayvite® and Vitamin K_1 Oxide Administered Intravenously to Change Prothrombin Time from Longer than to Shorter than That of 10 Per Cent Normal Control Plasma*

Material and Dose		Patient	Hours	Average, Hr.
Menadione sodium bisulfite U. S. P., mg.	64	L. A.	120	27
	120	L. H.	12	
	120	J. D.	8	
	180	G. H.	8	
"Synkayvite"	100	M. M.	10	14
	275	W. G.	18	
	340	W. S.	12	
	500	W. R.	18	
	500	C. D.	10	
	500	J. G.	18	
Vitamin K_1 oxide	100	W. M.	2	4
	100	L. L.	8	
	600	L. A.	6	
	500	W. R.	2	
	500	K. R.	4	
	2,000	M. Z.	2	

each) an average of 4 hours elapsed before the prothrombin time became shortened to less than that of 10 per cent normal plasma. The grouping of results was good (table 2), the shortest time interval being 2 hours (3 patients) and the longest, 8 hours (1 patient). Although the number of patients considered is small, the results, nevertheless, are striking. In none of the subjects treated with vitamin K_1 oxide was the time interval as long as the averages for the other two groups; and only in the case of 1 patient treated with vitamin K_1 oxide (who required 8 hours) did the results coincide with those for any of the patients treated with synkayvite® and menadione sodium bisulfite.

Comparison of These Agents in the Same Patient.—Figure 6 illustrates the efficacy of administration of equal amounts of synkayvite® and vitamin K_1 oxide to the same patient (W. R., a 70 year old man

with herpes zoster). The effect of synkayvite® was studied after five daily doses (totaling 1,100 mg.) of dicumarol® had prolonged his prothrombin time beyond that of 10 per cent normal plasma. Three days elapsed after the intravenous administration of 500 mg. of synkayvite® before his prothrombin time was shortened to less than that of 30 per cent normal plasma. After a rest period of 6 days from the last dose of dicumarol® (on the final 2 days his prothrombin time was equal to that of undiluted control plasma) he was given four daily doses (900 mg.) of dicumarol,® resulting in prolongation of the prothrombin time to a point equivalent to that of the previous episode. At this time he was given 500 mg. of vitamin K_1 oxide intravenously. In 8 hours his prothrombin time was equal to that of the undiluted control.

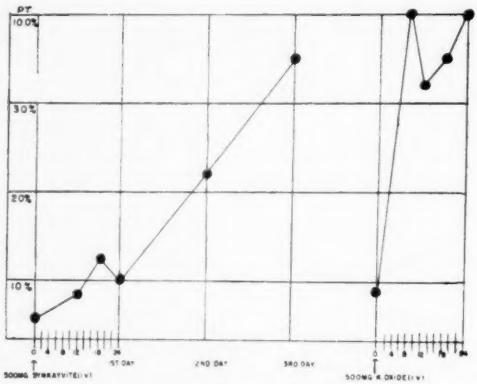

Fig. 6.—Comparison of equal amounts of synkayvite® and vitamin K_1 oxide (5.0 mg.) in the treatment of hypoprothrombinemia induced on two occasions by equivalent doses of dicumarol.® PT indicates prothrombin time.

The influence of vitamin K_1 oxide on prolonged prothrombin time as compared with that of a standard intravenous dose of menadione sodium bisulfite is illustrated in figure 5. The patient (L. A., a woman aged 43, with dementia paralytica) received two daily doses (500 mg.) of dicumarol,® which prolonged her prothrombin time beyond that of 10 per cent normal plasma. She received 64 mg. of menadione sodium bisulfite intravenously, which appeared to have a minor, evanescent effect. She was observed for five days after this treatment, the prolongation of prothrombin time persisting. She was then given 600 mg. of vitamin K_1 oxide intravenously, and in 9 hours her prothrombin time was within 2 seconds of that of undiluted normal plasma. The

abrupt increase in her prothrombin leaves little doubt that vitamin K_1 played a significant role in this change.

Toxic Symptoms of Menadione Sodium Bisulfite, Synkayvite® and Vitamin K_1 Oxide.—There was no laboratory or objective evidence that any of the antagonists of dicumarol® had caused toxic reactions. The only subjective effect of vitamin K_1 oxide was mild euphoria, as seen in 1 patient, possibly the result of the ethyl alcohol used to dissolve the material. Of 7 patients receiving 180 mg. of menadione sodium bisulfite in a single dose, 3 complained of a sensation of heat and internal "burning," which started at the termination of the injection. These complaints passed off within 5 minutes. Of the 7 patients given synkayvite®, 1 complained of severe generalized headache, tinnitus

TABLE 3.—*Variations in Prothrombin Times of Normal Control Plasmas, Undiluted and Diluted with 0.85 Per Cent Sodium Chloride Solution to Plasma Concentrations of 30, 20 and 10 Per Cent*

Patient	No. of Observations	Prothrombin Time	Plasma Dilutions			
			Undiluted	30%	20%	10%
D. J.	33	Average	15.9	22.6	28.9	50.2
		Shortest	11.4	18.5	21.0	25.3
		Longest	21.1	30.1	37.6	77.9
P. S.	24	Average	17.0	26.3	35.2	56.5
		Shortest	12.0	19.5	25.0	40.5
		Longest	21.6	32.9	48.7	96.0
M. G.	20	Average	15.3	23.0	30.7	54.1
		Shortest	11.7	18.4	24.8	40.2
		Longest	23.0	33.5	37.6	89.5

and tingling of the face after 100 mg. had been injected. The injection was stopped, and all these symptoms disappeared within 5 minutes.

Variability of Controls.—The reliability of normal controls as an index of the dicumarol® effect was investigated. Table 3 presents the average, shortest and longest prothrombin times for the 3 normal subjects used most frequently. The overlapping of the shortest prothrombin times of relatively dilute plasma and the longest times of more concentrated plasma is demonstrated. It is probable that the variability in prothrombin times from day to day in the same subjects is related to differences in the lots of thromboplastin used.

Thirty-three observations were made (in a period of three months) on samples of plasma withdrawn from 1 of the subjects (table 3). Analysis of the prothrombin times of his undiluted plasma shows that of the 33 observations, 10 (30 per cent) varied by no more than ± 1.5 seconds from the average of 15.9 seconds. Identical results were obtained on analysis of the determinations made on the same 33 samples of plasma diluted to 30 and 20 per cent with isotonic saline solution;

i.e., 30 per cent of these readings were within ± 1.5 seconds of the average times (22.6 and 28.9 seconds, respectively). When the prothrombin times for these same samples diluted to 10 per cent were examined, the situation was decidedly different. Of the 33 samples, only 2 (6 per cent) had prothrombin times within ±1.5 seconds of the average of 50.2 seconds. It was only after the variability was increased to ±8 seconds that 30 per cent of the samples fell within the variability range of 1.5 seconds. It is also noteworthy that poor checks were obtained with duplicate samples of plasma diluted to 10 per cent, as previously described. In many instances the clot was poorly defined and appeared so slowly that experienced observers could not agree on the end point. With plasma diluted to 30 and 20 per cent, duplicate samples checked satisfactorily. That this difficulty is not due to lack of prothrombin is shown by the adequate clot which forms when an estimation of prothrombin is made on the undiluted plasma of a patient under the dicumarol® effect. Though many of these plasmas had prothrombin times longer than that of normal plasmas diluted to 10 per cent, the clot, when it did form, appeared quickly and definitely enough to permit good checks.

The necessity of using several normal controls in assessing the degree of hypoprothrombinemia has been emphasized.[9] It is not infrequently found, when two normal plasmas are examined in parallel, that the prothrombin time of a dilute sample of one may be shorter than that of a more concentrated specimen of another. Our data illustrate this possibility. On 83 days during a period of 3 months, observations were made on various groups of 3 normal subjects. Analysis of these groups for discrepancies in the prothrombin times of individual subjects revealed that overlapping occurred in a significant number of instances; that is, the prothrombin time of one plasma was longer than the prothrombin time of a higher dilution of another plasma. On 4 of the 83 days the prothrombin time of one subject's 10 per cent plasma was shorter than that of another's 20 per cent plasma. On 12 occasions the prothrombin time of a sample of 20 per cent plasma was shorter than that of a sample of 30 per cent plasma. On 2 days the prothrombin time of a specimen of 30 per cent plasma was shorter than that of a sample of undiluted plasma. On no occasion, however, was there such a discrepancy between the prothrombin time of one of the normal plasmas and the average for the group to which it belonged.

9. Aggeler, P. M.; Howard, J.; Lucia, S. P.; Clark, W., and Astaff, A.: Standardization of the Quick Prothrombin Test, with Reference to Statistical Significance of Variations in Prothrombin Concentration with Use of Stable Thromboplastin of High Potency, Blood **1**:220 (May) 1946.

COMMENT

Comparison of Effect of Menadione Sodium Bisulfite, Synkayvite® and Vitamin K_1 Oxide.—Few comparative studies have been made on the synthetic vitamin K substances and substitutes. The importance of such a study, and the possibility that remarkable pharmacologic differences among these substances might exist were brought out by Fieser [10] in his description of the compounds with vitamin K activity. That certain fundamental differences among these compounds do exist was ascertained by Molitor and Robinson,[11] who demonstrated that whereas 2-methyl-1,4-naphthoquinone (menadione U. S. P.) had an oral lethal dose of 0.5 Gm. per kilogram in 50 per cent of mice, rats and chicks, 50 times this amount of vitamin K_1 had no lethal effect. Similar observations were made by these authors in chronic experiments. Thus, pharmacologic, as well as chemical, variations in these compounds are established, and it is no longer reasonable to speak of treating a patient with vitamin K without considering which of the compounds commonly included under this designation is used.

Smith, Ivy and Foster, in 1943,[12] studied the vitamin K activity and general pharmacologic and toxic reactions of synkayvite® and menadione sodium bisulfite U. S. P. (2-methyl-1,4-naphthohydroquinone sodium bisulfite complex) in rats. Richards and Shapiro, in 1945,[13] reported observations on the effect of menadione sodium bisulfite and synkayvite® in a study of their toxicity in animals and of their action in conjunction with salicylate therapy in man. Almquist and Klose [14] compared the effects of vitamin K_1 and menadione U. S. P. by oral administration of these substances to vitamin K–depleted chicks and concluded that vitamin K_1 had 38 per cent of the activity of the latter agent. These, and other, studies are summarized by Almquist.[15] A comparison of the results obtained using phthiocol (2-methyl-3-hydroxy-1, 4-naphthoquinone), menadione U. S. P. and 4-amino-2-methyl-naphthol hydrochloride was made on 26 patients with hypoprothrombinemia (not

10. Fieser, L. F.: The Chemistry of Vitamin K, Ann. Int. Med. **15**:648 (Oct.) 1941.

11. Molitor, H., and Robinson, H. J.: Oral and Parenteral Toxicity of Vitamin K_1, Phthiocol and 2-Methyl-1,4-Naphthoquinone, Proc. Soc. Exper. Biol. & Med. **43**:125, 1940.

12. Smith, J. J.; Ivy, A. C., and Foster, R. H. K.: The Pharmacology of Two Water-Soluble Vitamin K-Like Substances, J. Lab. & Clin. Med. **28**:1667 (Nov.) 1943.

13. Richards, R. K., and Shapiro, S.: Experimental and Clinical Studies on the Action of High Doses of Hykinone and Other Menadione Derivatives, J. Pharmacol. & Exper. Therap. **84**:93 (June) 1945.

14. Almquist, H. J., and Klose, A. A.: Antihemorrhagic Activity of 2-Methyl-1,4-Naphthoquinone, J. Biol. Chem. **130**:787 (Oct.) 1939.

15. Almquist, H. J.: Vitamin K, Physiol. Rev. **21**:194 (Jan.) 1941.

induced by dicumarol®) by Aggeler, Lucia and Goldman.[16] Butt, Snell, Osterberg and Bollman[17] investigated the use of 1,4-dehydroxy-2-methyl-3-naphthaldehyde, menadione U. S. P. and a compound thought to be a sodium salt of 3-sulfonic acid of 2-methyl-1,4-naphthoquinone in the treatment of 30 patients exhibiting hypoprothrombinemia. None of these investigations was concerned with dicumarol.®

Few studies have been made comparing the ability of various substances with vitamin K activity to reverse the effect of dicumarol,® and none of these has dealt with their efficacy in human subjects. Brodie and co-workers[18] reported in 1945 on the inhibition of dicumarol® hypoprothrombinemia in rats by menadione U. S. P., phthiocol and the 2,3 oxide of menadione U. S. P., and found them all effective, menadione being slightly more so than the others. Meunier and Mentzer[19] used 2-methyl-1,4-naphthoquinone, as well as a water-soluble derivative, in a study of the inhibition of dicumarol® hypoprothrombinemia in rabbits, but did not make comparative tests.

Data concerning the effect of dicumarol® on the prothrombin time cannot be used without considering species differences. Results obtained in the treatment of other types of hypoprothrombinemia cannot be transposed by analogy to those resulting from administration of dicumarol.® This is obvious when one considers the marked quantitative difference in amounts of preparations with vitamin K activity necessary in order to reverse the dicumarol® effect, as contrasted with other types of reversible hypoprothrombinemia.[20]

The observations of Cromer and Barker and others of their group[21] have formed a large part of the basis for the administration of antidotes

16. Aggeler, P. M.; Lucia, S. P., and Goldman, L.: Effect of Synthetic Vitamin K Compounds on Prothrombin Concentration in Man, Proc. Soc. Exper. Biol. & Med. **48**:689 (April) 1940.

17. Butt, H. R.; Snell, A. M.; Osterberg, A. E., and Bollman, J. L.: Treatment of Hypoprothrombinemia: Use of Various Synthetic Compounds Exhibiting Antihemorrhagic Activity (Vitamin K_1 Activity), Proc. Staff Meet., Mayo Clin. **15**:69 (Jan. 31) 1940.

18. Brodie, D. C.; Hiestand, W. A., and Jenkins, G. L.: The Inhibitory Effect of Certain Naphthoquinones on the Hemorrhagic Action of Dicumarol, J. Am. Phar. A. (Scient. Ed.) **34**:73 (March) 1945.

19. Meunier, P., and Mentzer, C.: L'essai des produits antihémorragiques (vitamin K) sur le lapin atteint de la maladie du mélilot gâté Bull. Soc. chim. biol. **24**:371 (Dec.) 1942.

20. An exception to this statement is the case of idiopathic hypoprothrombinemia reported from this clinic (Lewis, J., and Bennett, I. L., Jr.: Clinical Hypoprothrombinemia: A Study of Factors A and B of Prothrombin (abstract), J. Clin. Investigation **26**:1187 [Nov.] 1947).

21. (*a*) Cromer, H. E., and Barker, N. W.: The Effect of Large Doses of Menadione Bisulfite (Synthetic Vitamin K) on Excessive Hypoprothrombinemia Induced by Dicumarol, Proc. Staff Meet., Mayo Clin. **19**:217 (May 3) 1944. (*b*) Barker, Cromer, Hurn and Waugh.[2] (*c*) Barker, Hines, Kvale and Allen.[6a]

to dicumarol.® Prior to the present series, their study of the treatment of the effect of excessive amounts of dicumarol® is the largest reported. They [21a] gave menadione sodium bisulfite U. S. P. (hykinone®), usually in a single intravenous dose of 64 mg., to 37 patients who had excessive hypoprothrombinemia after administration of dicumarol,® i.e., a prothrombin time longer than that of 10 per cent normal plasma. Two of their patients did not respond to this treatment, and 3 others responded with minimal lowering of the prothrombin time within 18 hours. These workers emphasized that they had made no attempt to bring the prothrombin time entirely back to normal but that their aim had been merely to bring it within therapeutically effective limits. Thirty-five of their 37 patients responded to the administration of menadione sodium bisulfite with a shortening of prothrombin time to less than that of 10 per cent normal plasma within 18 hours. Fifty-nine per cent of their patients returned to a prothrombin time which was shorter than 35 seconds (20 per cent normal prothrombin time). No record was made of how many of their patients had shortening of the prothrombin time to a level equivalent to that of a 30 per cent normal plasma.

Cromer and Barker did not compare menadione sodium bisulfite with any other dicumarol® antidote. Thus, their study differed from the present investigation in that their aim was to return the prothrombin time from longer than that of 10 per cent normal plasma to shorter than that of 10 per cent normal plasma; ours was to bring the prothrombin time from longer than that of 20 per cent normal to shorter than that of 30 per cent normal plasma. Our other object was the comparison of three of the most active compounds with a vitamin K effect which could be administered intravenously. It should be noted that no attempt was made to compare equimolecular amounts or equal weights of these compounds. Amounts were given which had previously been shown to be safe.

The data for 16 of our patients could be analyzed in a manner similar to that of Cromer and Barker. Our results are substantially in agreement with theirs; but, in addition, they demonstrate the notably greater efficacy of vitamin K_1 oxide (table 2).

The reason for investigating the ability of these drugs to shorten the prothrombin time to above 30 per cent of normal, i. e., within the so-called clottabe range, is illustrated by a case reported by Bauerlein.[22] After the patient had received 100 mg. of dicumarol® for 13 successive days and the prothrombin concentration was 18 per cent,

22. Bauerlein, T. C.: Failure of Vitamin K as an Antidote in Dicumarol Poisoning, Rocky Mountain M. J. **42**:950 (Dec.) 1945.

he bled continuously from the genitourinary tract for 10 days and from the colon for the last 5 days. This patient had received 60 mg. of menadione sodium bisulfite U. S. P. (hykinone®) on the third, fourth and fifth days and had a prothrombin time of 8 minutes on the fifth day of bleeding.

Development and Use of Vitamin K_1 Oxide.—In 1939, Frank, Hurwitz and Seligman [23] described the use of synthetic vitamin K_1, orally and intravenously, in the treatment of 2 patients with obstructive jaundice. Ten milligram doses were used, and a return to a normal prothrombin level occurred within 4 hours. In 1941 [24] this group discussed the intravenous administration of vitamin K_1 (2-methyl-3-phytyl-1,4 napthoquinone) to 5 patients with obstructive jaundice, 2 with biliary fistula, 4 with hepatitis and 3 newborn infants with prothrombin deficiency and bleeding. Some of these patients and a few others with these illnesses were treated with menadione U. S. P. and a water-soluble sulfuric ester of 2-methyl-1,4-naphthohydroquinone U. S. P. given intravenously. A single 10 mg. dose of the latter given intravenously in cases of obstructive jaundice and biliary fistula produced a more rapid and prolonged effect than any other substance reported up to that time. Single doses of 0.25 mg. of vitamin K_1 were enough to result in rapid cures of hemorrhagic disease of newborn infants. The prothrombin deficiency of hepatic failure did not respond satisfactorily to 10 mg. doses of vitamin K_1.

The greater stability of vitamin K_1 oxide was utilized by Davis, Frank, Hurwitz and Seligman, who in 1943 [25] first described the clinical use of this substance (in 6 and 10 mg. doses) intravenously in the successful treatment of 2 patients with hypoprothrombinemia due to obstructive jaundice.

The effect of vitamin K_1 oxide on the prevention and treatment of hypoprothrombinemia induced by large single doses of dicumarol® was reported in 1943 by Davidson and MacDonald.[8] In 4 of the 5 patients studied, a marked effect was shown to be exerted by dicumarol.® In 3 patients, hypoprothrombinemia induced with single 0.5 and 1.0 Gm. doses of dicumarol® was treated with 200, 350 and 450 mg. of vitamin K_1 oxide, given intravenously. In 1 of these patients the prothrombin

23. Frank, H. A.; Hurwitz, A., and Seligman, A. M.: Treatment of Hypoprothrombinemia with Synthetic Vitamin K_1: Report of Two Cases, New England J. Med. **221**:975 (Dec. 21) 1939.

24. Seligman, A. M.; Hurwitz, A.; Frank, H. A., and Davis, W. A.: Intravenous Use of Synthetic Vitamin K_1, Surg., Gynec. & Obst. **73**:686 (Nov.) 1941.

25. Davis, W. A.; Frank, H. A.; Hurwitz, A., and Seligman, A. M.: Intravenous Use of Vitamin K_1 Oxide, Arch. Surg. **46**:296 (Feb.) 1943.

concentration returned to normal in 14 hours, and in another, in 24 hours. The patient given 200 mg. showed no response.

The treatment of 1 human subject who was given twelve daily doses of 500 to 1,000 mg. of dicumarol® was outlined by Lucia and Aggeler in 1944.[26] His prothrombin concentration fell to below 10 per cent of normal on the third, fifth and seventh days and after this was even more prolonged. Three days after the last dose of dicumarol,® he was given 500 mg. of vitamin K_1 oxide intravenously. This treatment resulted in dramatic elevation of the prothrombin level, beginning in 4 hours, and recovery in 24 hours from the hemorrhagic manifestations which had been present for the previous five days. The doses of dicumarol® used in the treatment of this patient were much larger than those in any series reported recently.

In 1945, Davidson, Freed and MacDonald[7] reported the results of their investigations of the effect of large doses (0.5 to 3.0 Gm.) of vitamin K_1 oxide on the coagulation time of the blood of 10 patients given large amounts of dicumarol® (initial doses of 0.5 to 1.0 Gm., followed by 0.2 Gm. daily). Three and a half to 36 hours was required before the coagulation time of the blood returned to normal. As in the last two reports cited, these doses of dicumarol® were greatly in excess of those generally regarded as therapeutically effective in the prevention and treatment of thromboembolic disease.

In 1947, Lewis and Bennett[20] presented the details of the treatment of a patient with severe, acute idiopathic hypoprothrombinemia. Despite the administration of 2,700 mg. of synkayvite® in 36 hours (two doses of 1,000 mg. and one dose of 500 mg. were given intravenously), and multiple transfusions of blood and plasma, this patient's prothrombin time was improved only temporarily and incompletely (never shorter than 10 per cent normal) until two days after admission, when she received 1 Gm. of vitamin K_1 intravenously. A few hours later her prothrombin time was within a safe range, and it has remained normal since 5 hours after she received this agent.

A result of administration of vitamin K_1 oxide to which attention should be called is the difficulty of obtaining a satisfactory dicumarol® effect in a patient who has recently received it.[27] That this is a matter

26. Lucia, S. P., and Aggeler, P. M.: Treatment of Dicoumarol-Induced Hypoprothrombinemic Hemorrhage with Vitamin K_1 Oxide, Proc. Soc. Exper. Biol. & Med. **56**:36 (May) 1944.

27. James, D. F.; Scheinberg, P., and Butler, J. J.: Clinical Studies on Dicumarol Hypoprothrombinemia and Vitamin K Preparations: III. Resistance to Dicumarol Following the Administration of Vitamin K_1 Oxide, to be published.

of practical concern is demonstrated by the remarkable unresponsiveness to dicumarol® of patients who have recently been given vitamin K_1 oxide. As has previously been shown, the amount of dicumarol® needed again to prolong the prothrombin time to beyond that of 20 per cent normal plasma is relatively unchanged if menadione sodium bisulfite has recently been given or if the patient has been allowed to recover without treatment. If vitamin K_1 oxide has recently been administered, on the other hand, the amount of dicumarol® must be increased twofold or threefold. This phase of the study is the subject of a separate report.[27]

Variability of Controls.—Our data support the findings of Aggeler and his co-workers,[9] who emphasized the importance of using several normal controls (they recommended at least 5) in standardizing a specimen of thromboplastin and setting up a curve of prothrombin concentration against which the prothrombin time of a patient may be checked. In this study, we used commercially obtained thromboplastin and checked the prothrombin time of our patients against the average of 3 normal controls. The necessity of this plan in the safe management of dicumarol® therapy is emphasized by our finding of significant discrepancies in prothrombin time among normal plasmas on 14 of 83 days during which observations were made. Our observations on multiple sampling for 1 normal subject indicate that the prothrombin determination as here outlined is satisfactory until dilution with saline solution is carried to the 10 per cent range. At this level clot formation often becomes inadequate, probably principally as a result of dilution of fibrinogen. The one stage assay of prothrombin has been shown to tbe influenced by fibrinogen concentration.[28] Tagnon [29] added fibrinogen to the clotting mixture in order to obtain accurate readings for prothrombin time (when fibrinogen as well as prothrombin were diluted by experimental procedures). Nitsche and his associates [30] added fibrinogen to plasmas diluted with saline solution in order to obtain more accurate prothrombin times in the dilute ranges. Rosenfield and Tuft [31] stated the belief that the dilution of plasma with

28. Deutsch, H. F., and Gerarde, H. W.: Biophysical Studies of Blood Plasma Proteins: V. The Effect of Fibrinogen on Prothrombin Time, J. Biol. Chem. **166**:381, 1946.

29. Tagnon, H. J.: Nature of the Mechanism of Shock Produced by Injection of Trypsin and Thrombin, J. Clin. Investigation **24**:1 (Jan.) 1945.

30. Nitsche, G. A., Jr.; Gerarde, H. W., and Deutsch, H. F.: Prothrombin Time Studies on Human Beings and Experimental Animals, J. Lab. & Clin. Med. **32**:410 (April) 1947.

31. Rosenfield, R. E., and Tuft, H. S.: Estimation of Prothrombin Level from Prothrombin Time, Am. J. Clin. Path. **17**:405 (May) 1947.

saline solution to a concentration in the neighborhood of 10 per cent introduces marked and uncontrollable variations in the method. The substitution of prothrombin-free plasma [32] as a diluent in the place of saline solution is being investigated in this laboratory.

CONCLUSIONS

In order to establish a broader clinical basis for the control of the dicumarol® (3,3'methylene-bis-[4-hydroxycoumarin]) effect, menadione sodium bisulfite, synkayvite® (tetrasodium salt of 2-methyl-1,4-naphthohydroquinone diphosphoric acid ester) and vitamin K_1 oxide (oxide of 2-methyl-3-phytyl-1,4-naphthoquinone) were administered in large single doses to patients with hypoprothrombinemia induced by dicumarol.® The efficiency of these substances was estimated on the basis of two factors: the time elapsing between the administration of the drug and the conversion of pronounced to moderate hypoprothrombinemia, and the time elapsing after administration of the agent until the appearance of a prothrombin level consistent with intravascular clotting.

Vitamin K_1 oxide was strikingly more effective in both respects. For 26 patients given 0.5 Gm. or more of this material intravenously the prothrombin time arrived and stayed at a level lower than that of 30 per cent normal plasma in an average time of 13 hours. When menadione sodium bisulfite (64 to 180 mg.) was given intravenously to 19 patients, this shortening of the prothrombin time was achieved in an average period of 4.7 days. When synkayvite® (100 to 500 mg.) was given intravenously to 6 patients, an average time of 5.3 days elapsed. Six patients with severe hypoprothrombinemia who were treated with 0.1 Gm. or more of vitamin K_1 oxide required an average of 4 hours to achieve a prothrombin concentration within what is generally regarded as a safe range.

An analysis of the time required for achievement of dicumarol® effect shows that about 1 of every 5 patients required five or more days to achieve significant therapeutic effect from dicumarol® in the usual doses.

The requirement of an individual subject for dicumarol® is approximately predictable on the basis of the degree of his previous responsiveness to the drug. An exception to this situation occurs shortly after the administration of vitamin K_1 oxide, after which patients are relatively insensitive to dicumarol.®

32. Barker, Cromer, Hurn, and Waugh.[2] Rosenfield and Tuft.[31] Tanturi, C. A., and Banfi, R. F.: Improved Method for Determination of Plasma Prothrombin, J. Lab. & Clin. Med. **31**:703 (June) 1946.

An analysis of normal control values in a large number of determinations reveals their variability and the necessity of using several controls if a proper prothrombin dilution curve is to be derived. The great variability of prothrombin times of plasma diluted to 10 per cent concentration with saline solution is shown, and procedures designed to correct the main deficiency, that of fibrinogen, are discussed.

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ENDOCARDITIS IN "MAIN LINE" OPIUM ADDICTS

Report on Eleven Cases

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THE possibility that intravenous injection of opium in addicts might serve as a means of entry for organisms that could cause endocarditis was suggested by Lutembacher [1] more than thirty years ago, when he wrote of *"une injection intraveineuse malpropre."* A review of almost all the cases of endocarditis reported in English in the past thirty years, however, shows that venipuncture for the injection of opium or its derivatives was a possible factor in only 12 instances (table 1). An interesting group of 11 such cases, involving patients observed in a short period, forms the basis of this paper (table 2).

METHOD OF ADMINISTRATION OF DRUG BY ADDICTS

The method of administration of opium employed by addicts lends itself to the introduction of organisms into the blood stream. The equipment of an addict consists of an ordinary medicine dropper and a hypodermic needle, with a bit of cigaret paper or a segment of a catheter as an adapter. The opium is dissolved in water by heating in a spoon, and the solution is then filtered two or three times through cotton until it is clear. No attempt is made to sterilize the drug, the equipment or the site of injection, any of which may serve as a source of contamination by organisms. Groups of addicts may use the same equipment; infection of husband and wife with the same bacteria has been reported.[2] In fact, an outbreak of malaria in addicts was attributed to the communal use of equipment.[3] It is interesting, also, to note that the first cases of malaria in narcotic addicts in this country were reported

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1. Lutembacher, R.: Endocardite infectieuse secondaire des cardiaques, Presse méd. **26**:546-548 (Oct. 24) 1918.

2. Hussey, H. H.; Keliher, T. F.; Schaefer, B. F., and Walsh, B. J.: Septicemia and Bacterial Endocarditis Resulting from Heroin Addiction, J. A. M. A. **126**: 535-538 (Oct. 28) 1944.

3. Most, H.: Falciparum Malaria in Drug Addicts: Clinical Aspects, Am. J. Trop. Med. **20**:551-567 (July) 1940.

by Geiger [4] from the San Francisco Hospital. In view of such carelessness in self administration of drugs, it is surprising that there are not more infections, although cutaneous abscesses do occur frequently among those addicts who use the subcutaneous route for injection.

Opium addicts become very adept at the taking of opium by intravenous injection, but repeated venipuncture leaves the telltale dark, deep, pitted linear scars over the antecubital and other veins of the upper extremity. Eventually, the veins become so scarred that it is impossible

TABLE 1.—*Reported Cases in Which Endocarditis Apparently Followed Venipuncture for the Injection of Narcotic Agents*

Observer	Organism	Number of Cases	Valves Involved	Comment
Kearns, J. J.: Arch. Path. **21**: 839-843 (June) 1936	Pseudomonas aeruginosa (Bacillus pyocyaneus)	1	Aortic and mitral	
McMillan, R. L., and Wilbur, E. L.: J. A. M. A. **109**: 1194-1195 (Oct. 9) 1937	Hemolytic type of Staphylococcus aureus	1	Aortic and mitral	Syphilitic aortitis and valvulitis
Polayes, S. H., and Emmons, C. W.: J. A. M. A. **117**: 1533-1535 (Nov. 1) 1941	Candida (Monilia) parakrusei	1	Aortic	
Wikler and others [6]	Candida parakrusei	1	Mitral	
Helpern, M., and Weiner, A. A., cited by Wikler and others [6]	Candida parakrusei	2	Not reported	
Peery, T. M., cited by Wikler and others [6]	Candida guilliermondi	1	Not reported	
Hussey and others [2]	Pseudomonas aeruginosa (Bacillus pyocyaneus)	1	Aortic	
	Staphylococcus aureus	3	Tricuspid	
	Staphylococcus aureus	1	?	

to locate and puncture them, and the addict must resort to other routes of administration or must abandon opium for another drug.

ADDITIONAL FACTOR IN DEVELOPMENT OF BACTERIAL ENDOCARDITIS IN PERSONS ADDICTED TO OPIUM

The fact that all patients in the present series were seen in a three year period is an interesting one. On the Stanford University service of the San Francisco Hospital, in the ten year period from 1936 to 1946, about 110 patients who had bacterial endocarditis were observed, 30 of them after February 1944. In the same ten year period, 70 persons addicted to opium were seen, 19 since February 1944. Ten of the 19 had endocarditis.

4. Geiger, J. C.: Malaria in Narcotic Addicts, Correspondence, J. A. M. A. **98**:1494 (April 23) 1932.

TABLE 2.—*Summary of Clinical, Laboratory and Pathologic Data in 11 Cases of Bacterial Endocarditis Among Opium Addicts*

Case	Sex	Age, Yr.	Race	Date of Admission	Date of Death	Duration of Illness (Estimated)	Organism Isolated	Sensitivity to Penicillin, Units per Cc.	Valves Involved	Predisposing Heart Disease	Comment
1	M	32	W	2/10/44	2/13/44	1 mo.	Nonhemolytic streptococcus; Candida	.....	Necropsy: predominantly aortic valve, but small vegetation on mitral valve	Old mitral valvulitis?	Septic aneurysm adjacent to aortic ring
2	F	36	W	10/23/44	11/12/44	3 wk.	Nonhemolytic streptococcus	Growth.....1 Inhibition...5	Necropsy: predominantly aortic valve, with small mitral and tricuspid vegetations	None	
3	M	37	N	9/11/45	10/ 3/45	7 wk.	Nonhemolytic streptococcus	Growth.....3 Inhibition...3.5	Necropsy: predominantly aortic valve, with extension to, and perforation of, mitral valve	Small area of old scarring of aortic valve leaflet; syphilis of the aorta	Mitral insufficiency suspected clinically, with perforation of mitral valve leaflet
4	M	64	W	11/ 7/45	11/28/45	4 mo.	Nonhemolytic streptococcus	Growth.....1	Necropsy: aortic valve, with extension to membranous septum	Fibrous thickening of left auricular endocardium and uninvolved aortic cusps; calcification of bases of aortic cusps and of aortic ring	
5	M	38	W	1/ 4/46	3/ 3/46	6 mo.	Nonhemolytic streptococcus	Growth.....1 Inhibition...2	Clinical impression: aortic and (?) mitral	Syphilitic and rheumatic?	
6	M	40	N	2/19/46	2/27/46	3 wk.	Escherichia coli	.....	Necropsy: predominantly aortic valve, with extension to mitral valve	None	Aneurysmal tract extending from aortic sinus to epicardium at base of aorta and to medial wall of left atrium and base of anterior mitral cusp
7	M	49	W	5/ 5/46	6/15/46	7 wk.	Nonhemolytic streptococcus	Growth.....2.5 Inhibition...3	Clinical impression: aortic and (?) mitral	None	
8	F	28	N	5/25/46	Patient lived		Aerobacter aerogenes	.....	Clinical impression: mitral	None	Cured with streptomycin
9	M	52	N	5/29/46	6/24/46	7 wk.	None	.....	Clinical impression: aortic and (?) mitral	Syphilitic?	Unequivocal aortic endocarditis with femoral and cerebral emboli; blood cultures contaminated
10	M	46	W	6/14/46	9/ 4/46	5 mo.	Nonhemolytic streptococcus	Growth.....0.8 Inhibition...0.9	Necropsy: aortic and mitral	None	
11	M	65	W	2/ 3/47	6/ 7/47	5 mo.	Pseudomonas aeruginosa	.....	Necropsy: tricuspid	None	Improvement with streptomycin

The cause of the increased incidence of endocarditis among opium addicts during this period is not certain. Apparently, the opium itself was responsible.

The usual supply of opium from the Middle East and the Far East was interrupted by the war, and Mexico became the chief producer. The material obtained from that country was an incompletely refined gum opium, at times heavily adulterated. It resembled molasses or tar in appearance and consistency. The addicts noted that, despite filtration, a sediment would collect on the inside of the dropper after it had been used a few times, whereas formerly there had been none. Though the addicts had previously experienced chills only infrequently after injection, many were now forced to abandon the intravenous ("main line") route and to become "skin shooters" (addicts who inject drugs subcutaneously). In the latter procedure, at worst, only an abscess would develop. Other addicts gave up the opium habit, turning to alcohol or the barbiturates ("yellow jackets," "goof balls"). Although the addicts realized that some of their number were dying of a cardiac infection, they were unable to offer, or did not perceive, any reason for such infection.

No opportunity was offered to culture the opium used by these patients. In the case studied by Joachim and Polayes,[5] culture of the material being injected revealed the same organism as that obtained from the blood. Wikler and his group[6] were unable to culture the infecting organism from 11 samples of diacetylmorphine (heroin) but did obtain other fungi. For the most part the bacteria in the present series of cases were different from those in cases previously reported, but the types are of wide distribution. Dirty fingers or instruments could easily contaminate the crude opium, which, since it commonly is adulterated with some type of sugar, would then serve as a culture medium.

REPORT OF CASES[7]

CASE 1.—A white cleaner and presser, aged 32, was admitted to the hospital on Feb. 10, 1944.

History.—For twelve years the patient had been addicted to opium, which he took intravenously. He had had gonorrhea at the age of 17 years; his fingers, wrists and ankles had become red and swollen, but not painful. At the age of 20 years he had had a chancre, treated only with cautery. The patient had been well until a month before admission to the hospital, when he had first noticed an aching pain beneath the sternum and in the left anterior part of the thorax. This pain had persisted. He had taken no opium for three weeks

5. Joachim, H., and Polayes, S. H.: Subacute Endocarditis and Systemic Mycosis (Monilia), J. A. M. A. **115**:205-208 (July 20) 1940.

6. Wikler, A.; Williams, E. G.; Douglass, E. D.; Emmons, C. W., and Dunn, R. C.: Mycotic Endocarditis: Report of a Case, J. A. M. A. **119**:333-336 (May 23) 1942.

7. Reports of the entire 11 cases are included in the reprints of this article.

before admission. Two weeks before entry a dry cough, dyspnea, orthopnea and edema of the ankles had developed. A physician had prescribed digitalis. The patient had had diarrhea for two or three days.

Physical Examination.—The patient was pale, emaciated, dyspneic and moribund. His temperature was 101 F. (38.3 C.) and his pulse rate was 120. There were 26 respirations per minute (Cheyne-Stokes type). Systolic blood pressure was 120 mm. of mercury; diastolic, 35 mm. There were a punctate hemorrhage in the lower conjunctiva of the left eye and a petechia, with a white center, in the upper lid. Distention of veins in the neck was moderate with the patient in the upright position. There were rales in the bases of both lungs posteriorly. The apical impulse and the area of cardiac dulness were situated 2 cm. lateral to the midclavicular line in the fifth intercostal space. The rhythm was regular. There was a loud, blowing systolic murmur over the whole precordium, extending to the vessels of the neck. A loud, decrescendo, blowing early diastolic murmur was heard throughout the area, being maximal along the left sternal border in the fourth and fifth intercostal spaces. There was an apical presystolic gallop or rumbling murmur. The edge of the liver was felt below the umbilicus. Free abdominal fluid was present. There was pitting edema of the ankles and lower legs. The calves were tender. The superficial veins of the upper extremities were thrombosed, scarred and pitted.

Laboratory Data.—The value for hemoglobin was 12.2 Gm. per hundred cubic centimeters of blood. Leukocytes numbered 14,600 per cubic millimeter of blood; polymorphonuclear leukocytes amounted to 82 per cent; lymphocytes, 16 per cent, and monocytes, 2 per cent. The urine was amber and slightly turbid; the specific gravity was 1.014 and the p_H 7.5. There were slight traces of albumin and acetone in the urine, but no sugar. A rare leukocyte or erythrocyte per field was seen with the high power objective. The result of the Wassermann-Kolmer test was doubtful; the reaction to the Mazzini test was positive. Culture of a specimen of blood yielded a nonhemolytic type of streptococcus. The value for blood urea was 59 mg. per hundred cubic centimeters.

A roentgenogram of the thorax disclosed bilateral, diffuse mottling of the lungs. Pleural thickening was seen between the upper lobe and the middle lobe of the right lung. The heart was enlarged in all diameters. In the electrocardiogram the duration of the QRS complex was from 0.10 to 0.12 second, and the complex was notched and slurred in lead I. The S-T segments in leads I and IV were depressed; the T waves in leads I and IV were inverted.

Course.—The patient received sulfadiazine U. S. P. in full doses, with morphine. His temperature remained about 101 F. (38.3 C.). He died on February 13.

Necropsy.—The aortic valve contained several large vegetations, especially on the anterior cusp, which was almost entirely destroyed. Near one coronary ostium was an opening leading to a cavity which measured 2 by 3 mm. and was adjacent to the aortic ring. On the mitral valve was a small, flat vegetation. Section of the vegetations disclosed, in addition to gram-positive and gram-negative cocci in pairs and chains, yeastlike bodies and gram-positive and gram-negative coarse, branching, segmented hyphae. Microscopically, there was slight fibrous thickening of the mitral valve, but there was no other evidence of preexisting rheumatic heart disease. The fungus on the mitral valve was not cultured, but because of its structure it was thought to be a species of Candida.

CASE 3.—A Negro gambler, aged 37, was admitted to the hospital on Sept. 11, 1945.

History.—The patient had been addicted to morphine for seventeen years. He had had a penile chancre twenty years before the present illness, and had been treated for ten months in 1943 with preparations of heavy metals; at that time the physician had been concerned about the patient's heart. There was no history of rheumatic fever. The patient had been well until a month before admission to the hospital, when he had first noticed increasing shortness of breath on exertion. Three weeks later his ankles had begun to swell. He had lost 20 to 25 pounds (9 to 11 Kg.) in two or three months.

Physical Examination.—The patient was a thin, ill appearing Negro; he was sweating profusely. His temperature was 99 F. (37.2 C.) and his pulse rate 92. Systolic blood pressure was 110 mm. of mercury; diastolic, 30 mm. Petechiae were not seen. The veins of the neck were slightly distended when the patient was in the upright position. The lungs were clear. The apical impulse of the heart was in the sixth intercostal space, almost at the anterior axillary line. The rhythm was regular. The pulmonic second sound was greater than the aortic second sound. The apical first sound was loud. There was a soft, blowing, apical systolic murmur. A high-pitched, blowing diastolic murmur, beginning with the second sound, was heard along the left sternal border and was transmitted throughout the precordium. At the apex there was a rumbling, crescendo presystolic murmur, which was not transmitted. The tip of the spleen was felt. Neither edema nor clubbing was present.

Laboratory Data.—The value for hemoglobin was 11.4 Gm. per hundred cubic centimeters of blood. Erythrocytes numbered 3,600,000 and leukocytes 9,800, per cubic millimeter. Polymorphonuclear leukocytes amounted to 62 per cent; lymphocytes, 31 per cent; basophils, 1 per cent, and monocytes, 6 per cent. The urine was clear, except for the centrifuged sediment, which contained 3 to 4 leukocytes and an occasional erythrocyte per field, with high power magnification. The result of the Wassermann-Kolmer test was negative; that of the Mazzini test was positive. Blood culture made eight times produced a nonhemolytic type of streptococcus, which was resistant to 3 units of penicillin per cubic centimeter but was inhibited by 3.5 units per cubic centimeter. The value for blood urea was 24 mg. per hundred cubic centimeters. A roentgenogram of the thorax and roentgenoscopy showed the heart, especially the left ventricle, to be enlarged; the left atrium was not enlarged. An electrocardiogram made on September 12 was normal.

Course.—The administration of morphine was continued. The patient received penicillin (320,000 units daily, to a total of 3,500,000 units) and sulfamerazine U. S. P. (the level was 12 mg. per hundred cubic centimeters of blood), but no change occurred in the low grade fever or in the results of blood culture. Occasional painful swellings appeared in the pads of the fingers. On September 29, severe dyspnea developed, and rales were heard over the whole chest. The veins of the neck were distended. A pronounced systolic thrill was present at the apex, with a murmur transmitted to the back and over the aortic area to the neck. The apical second sound was louder than the first. There was a protodiastolic gallop. The patient was given lanatoside C parenterally, but his condition did not improve. In the electrocardiogram, the P-R interval was 0.23 second; there was low voltage (amplitude 5 mm.) of the QRS complex in the limb leads, and the T in lead I was less than 1 mm. in height. The value for blood urea was 74 mg. per hundred cubic centimeters on September 29; two days later it was 217 mg. per hundred cubic centimeters. After a progressively downhill course, the patient died, on October 3.

Necropsy.—Vegetations had destroyed the aortic cusps; the cusps were perforated. Extension and perforation of the anterior cusp of the mitral valve were seen. Rheumatic lesions were not identified, but a small area of scarring was present on the leaflet of one aortic valve, suggesting previous valvular damage. Syphilitic involvement of the aorta was extensive.

CASE 8.—A Negro prostitute, 28 years of age, was admitted to the hospital on May 25, 1946.

History.—The patient had been addicted to the use of morphine for eight years; recently, she had been injecting an unrefined product intravenously. There was no history of rheumatic fever or syphilis. She said that she had been tired for several months, particularly in the afternoons. She had felt feverish, and spoke vaguely of palpitations and exertional dyspnea. Three days before her admission, diarrhea had developed; four or five stools were passed daily. The diarrhea had been followed with nausea and vomiting, but no pain.

Physical Examination.—The patient was a very thin apathetic, drowsy young Negro woman. Her temperature was 102.6 F. (39.2 C.); the pulse rate was 108 and the respiratory rate 20. Systolic blood pressure was 96 mm. of mercury; diastolic, 50 mm. Scarring was seen over the veins of the upper extremities. The scleras were intensely icteric. The tongue was red, with smooth edges. The veins in the neck were distended to a point 5 cm. above the clavicle with the patient in the supine position. The lungs were clear. The apical impulse was in the fifth intercostal space, 2 cm. inside the midclavicular line. Rhythm was regular. The sounds were of fair quality. The pulmonic second sound was greater than the aortic second sound. There was a grade 2, blowing systolic murmur, maximal at the lower left sternal border. The abdomen was flat and tight, with tenderness throughout and dulness to percussion 5 cm. below the right costal margin. Neither the edge of the liver nor that of the spleen was felt. There was no edema of the ankles.

Laboratory Data.—The value for hemoglobin was 12 Gm. per hundred cubic centimeters of blood. Erythrocytes numbered 4,100,000 per cubic millimeter and leukocytes 18,000. Polymorphonuclear leukocytes amounted to 80 per cent; lymphocytes, 16 per cent, and monocytes, 4 per cent. The specific gravity of the urine was 1.015; the reaction was acid. The result of the test for urobilinogen was positive in a dilution of 1:20 and negative in a dilution of 1:40. The result of the foam test for bile was 3 plus. In the centrifuged sediment, there were 4 to 8 leukocytes per field, under high power magnification, and no erythrocytes. The reaction to the Wassermann test was positive. Blood culture produced Aerobacter aerogenes, which was inhibited by 0.3 microgram of streptomycin per cubic centimeter. The value for blood urea was 141 mg. per hundred cubic centimeters. The icterus index was 53. The value for serum proteins was 7.5 Gm. per hundred cubic centimeters (albumin, 3.4 Gm.; globulin, 4.1 Gm.). A roentgenogram of the thorax showed the size of the heart to be within normal limits. The left hilar shadow was heavier than usual, but the parenchyma was clear. The electrocardiogram disclosed sinus tachycardia. The T wave in lead I was low.

Course.—The use of morphine was continued. The patient received fluids, dextrose, electrolytes and vitamins parenterally. Two days after her admission, her temperature increased to 106 F. (41.1 C.), and many white-centered petechiae were noted in the conjunctivas. Four days after her entry the oral administration of sulfadiazine U. S. P. was begun, supplemented with the intravenous use of sulfadiazine sodium U. S. P. The concentration of the drug in the blood reached

15 mg. per hundred cubic centimeters. Blood culture still yielded growth; showers of petechiae continued to appear, and low grade fever (with a temperature up to 102 F. [38.9 C.]) persisted. The administration of sulfadiazine was discontinued on June 15. The value for blood urea had decreased to 62 mg. per hundred cubic centimeters on May 27 and to 30 mg. per hundred cubic centimeters on June 3. The icterus index was 31 on May 29, 13 on June 3 and 6 on June 11. The number of leukocytes increased to 49,000 per cubic millimeter; polymorphonuclear leukocytes amounted to 84 per cent. The value for hemoglobin decreased to 7.6 Gm. per hundred cubic centimeters of blood on June 6, when a transfusion of whole blood was given. On June 17, the administration of 3 Gm. of streptomycin per day was started, given in divided doses at three hour intervals. Except for an interruption of twenty-one hours on June 27, when the drug was unavailable, administration was continued until July 9. Immediately after the institution of streptomycin therapy, the blood culture became sterile, remaining so after the cessation of therapy until the time of the patient's discharge; a total of twelve cultures had then been made. The patient's fever subsided; no further petechiae appeared, and her condition improved generally, objectively and subjectively. During the period of streptomycin therapy, the systolic murmur had become louder (grade 4), despite the absence of fever and the correction of the anemia; no additional murmurs had appeared, and there was no change in the blood pressure. The patient was discharged on July 31, at which time she was still receiving small rations of morphine. Otherwise, she was improved.

CASE 11.—A 65 year old white gambler entered the hospital on Feb. 3, 1947.

History.—The patient had for many years been addicted to the use of morphine, which he took intravenously. He said that he had not used morphine for twelve years, however, except for an injection of dihydromorphinone hydrochloride U. S. P. (dilaudid®) on Jan. 2, 1947, and one of morphine sulfate on January 5. He said that he had not had rheumatic fever or syphilis. Three weeks before the patient's entry, a very painful swelling of the right sternoclavicular articulation had developed; this had persisted until his admission to the hospital. There were no chills or fever. He had lost 25 pounds (11 Kg.); he attributed this loss to diminished appetite. He had been treated with intravenous injections by his physician without relief.

Physical Examination.—The patient was well developed and well nourished. He was holding his head to the left, and he winced at any attempt to touch his right shoulder or clavicle. His temperature was 102 F. (38.9 C.). His pulse rate was 100 and his respiratory rate 20. Systolic blood pressure was 130 mm. of mercury; diastolic, 75 mm. There were no petechiae on the skin or conjunctivas. The veins in the neck were not distended. The thorax was emphysematous. Rhonchi were heard throughout. The heart was not enlarged, and the rhythm was regular. The sounds were distant over the base of the heart. Murmurs were not present. The spleen was not palpable. Over the right sternoclavicular articulation was a tender swelling, which was red and warm. Old scarring was seen over the veins of the arms, with discoloration at a few recent sites of injection.

Laboratory Data.—The value for hemoglobin was 15.3 Gm. per hundred cubic centimeters of blood. Erythrocytes numbered 5,100,000 per cubic millimeter; leukocytes, 10,400. Polymorphonuclear leukocytes amounted to 92 per cent; lymphocytes, 7 per cent, and monocytes, 1 per cent. A catheterized specimen of urine was clear and amber; the specific gravity was 1.024. The p_H was 6.0. Neither albumin nor glucose was found. The centrifuged sediment contained no erythrocytes, but

2 or 3 leukocytes were noted per field, under high power magnification. The result of the Wassermann test was doubtful. Blood culture produced Pseudomonas aeruginosa, which was sensitive to 17.5 units of streptomycin per cubic centimeter but not to 16 units. Later, at another laboratory, it was noted that growth of the organism was not completely inhibited by 25 micrograms per cubic centimeter; by means of a special technic, large numbers grew in 50 micrograms of streptomycin per cubic centimeter. The value for blood urea was 32 mg. per hundred cubic centimeters. A roentgenogram of the thorax showed the heart and lungs to be normal.

Course.—The patient received no opiates. His temperature ranged from 101 to 103 F. (38.3 to 39.4 C.) for the first four days. On February 7, the administration of full doses of sulfadiazine U. S. P. and of penicillin (30,000 units intramuscularly every three hours) was begun. The fever decreased to some degree, and the sternoclavicular pain lessened slightly, but blood culture continued to yield growth. The administration of penicillin was discontinued on February 11. The spleen was palpated first on February 11; throughout the patient's illness it could usually be felt. On February 13, a little bloody material was aspirated from the sternoclavicular joint; from this material, Ps. aeruginosa was cultured. Roentgenograms of the joint revealed nothing abnormal. It was observed that the patient had not been taking all the sulfadiazine prescribed, the content in the blood being only 3 mg. per hundred cubic centimeters. On February 14, the dose of sulfadiazine was doubled, so that 2 Gm. was administered every four hours. The content of the drug in the blood did not increase to more than 7.4 mg. per hundred cubic centimeters, and on February 20, 5 Gm. of sulfamerazine sodium U. S. P. was administered intravenously. On February 21, the amount of this drug in the blood was 25 mg. per hundred cubic centimeters, but blood culture continued to yield growth. The patient then received 2 Gm. of sulfadiazine U. S. P. and sulfamerazine U. S. P. orally every four hours and 5 Gm. of sulfamerazine sodium U. S. P. intravenously daily, the concentration in the blood increasing to between 10 and 20 mg. per hundred cubic centimeters, but decreasing to as low as 5 mg. per hundred cubic centimeters on February 25, probably because of lack of cooperation on the part of the patient in taking the medication orally. Blood cultures, made almost daily, still yielded organisms. After a chill, followed by an increase in temperature to 105.6 F. (40.9 C.) the administration of sulfonamide drugs was discontinued, on February 25.

On February 26 the administration of streptomycin was begun; the initial dose was 0.75 Gm., given intravenously and intramuscularly. A total of 6 Gm. was administered intramuscularly on February 27 and 28, in four hour doses; 5 Gm. was given on March 1, and 4 Gm. was given on March 2 and again on March 3. The patient's temperature decreased to between 101 and 102 F. (38.3 and 38.9 C.) until March 4, and then to between 99 and 100 F. (37.2 and 37.8 C.) until March 8. Blood cultures carried out twelve and eighteen hours after the administration of streptomycin had been started yielded no growth. Culture carried out about twenty-four hours after the beginning of streptomycin therapy produced Ps. aeruginosa. When the report of this result was received, on March 3, the use of streptomycin was discontinued. The organism isolated, however, appeared to be a contaminant, for it was later found to be inhibited by streptomycin in concentrations of 2.6 units per cubic centimeter. Blood cultures carried out daily from February 28 until March 3, but not reported until after therapy had been stopped, yielded no growth. Culture was next made on March 6, producing Ps. aeruginosa, which was sensitive to streptomycin only in a concentration

of 17.5 units per cubic centimeter, as had been the organism initially tested. From March 8 until March 14, the patient had almost daily chills, with the temperature ranging from 104.5 to 106.5 F. (40.3 to 41.4 C.). On March 13, 14 and 17, he received, respectively, 12, 15 and 18 cc. of a 1 per cent solution of merbromin N. F. (mercurochrome®) intravenously. On March 15 and 16 his temperature was 100 F. (37.8 C.) and on March 17 it was 103 F. (39.4 C.), the blood cultures yielding growth each day.

On March 18, a second course of streptomycin was begun; 6 Gm. was administered intravenously each day, in divided doses at four hour intervals; this course was continued until March 29. On March 19 the concentration of streptomycin in the blood four hours after administration was 100 units per cubic centimeter. The temperature decreased promptly and ranged from 99 to 101 F. (37.2 to 38.3 C.) until April 12; it then remained about normal until April 20. Blood cultures on March 19 and 20 were sterile. Ps. aeruginosa, resistant to 70 units of streptomycin per cubic centimeter, was cultured from a specimen of blood on March 21. Blood cultures made almost daily after that date were sterile until April 24. On April 20 the patient had a chill, with a temperature of 103 F. (39.4 C.), and almost daily after that he had chills, with an increase in temperature to 105.5 F. (40.8 C.). Blood culture on April 30 yielded growth and continued to do so thereafter. The administration of penicillin and sulfadiazine was begun again in full doses, but chills and a temperature of 105.5 F. persisted.

The sternoclavicular arthritis subsided during the first month; loss of continuity of the articulation was noted later. Frequent and careful auscultation revealed no cardiac murmurs. Soon after the patient's admission the blood pressure decreased to about 80 systolic and 50 diastolic, remaining at that level, with no widening of the pulse pressure. A conjunctival petechia without a white center was observed on May 21. Roentgenograms of the thorax made at approximately monthly intervals revealed small, patchy areas of density, of a migratory nature. The value for hemoglobin at one time decreased to 10 Gm. per hundred cubic centimeters of blood, and whole blood was transfused. The urine was recorded as remaining clear, although Ps. aeruginosa was cultured from it several times. The patient's course was progressively downhill, with the development of extreme emaciation. He died on June 7.

Necropsy.—A 2 by 2.5 cm. vegetation was observed adhering to the chordae tendineae of the tricuspid valve. The other valves appeared normal, except that at the base of the aortic cusps considerable sclerosis was present, and the commissures of the aortic valves were agglutinated.

COMMENT

A species of Candida was observed once in the present series (case 1); it was the causative agent in nearly half the cases reported earlier. The infection with Candida was one part of a double infection; the other was caused by a nonhemolytic type of streptococcus. The infection with Candida was observed only on microscopic section. Case 1 was interesting also in that a true mycotic aneurysm was present. Septic aneurysms were noted in other cases.

Nonhemolytic streptococci were the infecting organisms in the majority of the cases; none were reported in the group reviewed earlier. Because of the apparent resistance of these particular organisms to heat,

applied in the preparation of the opium for injection, and because of the insensitivity of these organisms to penicillin, it has been suggested that they were enterococci. Penicillin in amounts sufficiently large to treat these patients was unavailable at the time. The clinical picture and course in all the cases of infection with these organisms were much the same. Case 3 is offered as an example in preference to the others only because of the apparently sudden development of mitral insufficiency.

The presence of A. aerogenes in the blood and the presence of petechiae and a systolic murmur which increased in intensity during the period of observation permitted the diagnosis of bacterial endocarditis in case 8. The use of streptomycin therapy resulted in cure, a feature unique in this series. Streptomycin was not available for trial in case 6, in which the infective organism was Esch. coli.

The tricuspid endocarditis due to Ps. aeruginosa in case 11 was not diagnosed prior to the death of the patient. There was no cardiac enlargement, and no murmur was heard at any time, despite frequent and careful auscultation throughout the unusually long course of the disease. The migratory areas of pulmonary density seen roentgenologically may have represented septic infarcts, although such lesions were not suspected clinically. Despite the temporary sterilization of the blood and the clinical improvement resulting from the use of streptomycin, treatment did not result in cure.

The aortic valve was involved in 9 of the 11 cases; the ease with which the murmur of aortic insufficiency is heard aids greatly in diagnosis. The aortic lesion was predominant in cases in which the mitral valve was also involved; involvement of the mitral valve appeared to be secondary. In case 3, extension had apparently taken place from the aortic to the mitral valve, with perforation and the appearance of a loud systolic murmur and of cardiac failure, with resultant mitral insufficiency. Clinical suspicion of involvement of the mitral valve stemmed from the detection of murmurs that might also have been interpreted as Flint murmurs, or as signs resulting from functional mitral insufficiency.

Preexisting heart disease, it would appear, was not necessary for the development of endocarditis, although some degree of fibrosis was found in otherwise uninvolved valvular leaflets. No definite rheumatic involvement was found in any case, although the evidence might have been lost with the almost complete destruction of the valves so frequently noted. The frequent pimp-prostitute relationship of such addicts is recognized; 9 of the patients were syphilitic. Although syphilitic heart disease may have been a predisposing factor, there was little to indicate that this had been true. Perhaps the normal heart valves finally succumbed to attack after bacteria had been repeatedly injected into the blood stream.

SUMMARY

Eleven instances of endocarditis in opium addicts who used the intravenous route of administration were recorded in a three year period. Interference with the supply of opium from the Middle East and the Far East during the recent war resulted in the importation of a crude opium from Mexico. It has been suggested that in the handling of the crude material without precautions as to sterility, bacteria gain entrance to the blood stream and give rise to endocarditis.

The causative organism in 7 of the 11 cases was a nonhemolytic type of streptococcus, resistant to penicillin. In 1 of these cases, a species of Candida also was present. Esch. coli was responsible in 1 case; no organism was isolated in another. The aortic valve was involved in these 9 cases; involvement of the mitral valve, when present, appeared secondary.

Streptomycin effected a cure in 1 case of endocarditis caused by A. aerogenes. The mitral valve was probably involved in this case. In 1 case a patient who had tricuspid endocarditis caused by Ps. aeruginosa survived for five months, despite only transient improvement resulting from streptomycin therapy.

No definite evidence of rheumatic, congenital or syphilitic heart disease was present in these cases. It is possible that in the particular type of endocarditis concerned the heart valves need not have been damaged previously and that normal valves may have become infected after repeated exposure to injected bacteria.

NOTE.—In October 1946, a 45 year old white man, who had been using opiates intravenously for many years, was admitted to the University of California service of the San Francisco Hospital for treatment of endocarditis, caused by Streptococcus faecalis. The organism was resistant to 9 units of penicillin per cubic centimeter. There was no history of syphilis or rheumatic fever. The patient died after five weeks in the hospital; his illness had lasted a total of about a year. The coroner reported endocarditis limited to the mitral valve.

In June 1947, a 38 year old white woman, who had been a morphine addict for many years, entered the San Francisco Hospital on the University of California service. She had endocarditis, caused by Str. faecalis, involving the aortic valve; the endocarditis persisted, despite treatment with penicillin and streptomycin. Pyelonephritis also was present. The patient died of uremia and congestive heart failure, almost seven months after the onset of her illness. Necropsy was not performed.

ASYMPTOMATIC MYOCARDIAL INFARCTION

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EVER since 1700, when Bonetus [1] first demonstrated the correlation of dyspnea, sudden death and calcified coronary vessels, the study of disease of the coronary arteries has commonly been related to the study of severe symptoms in the patient. It remained for Herrick,[2] as late as 1912, finally to present a complete clinical description of the syndrome of sudden occlusion of the coronary arteries. Little was accomplished in the evolution of this important medical concept in the interval between these two dates. The delay constitutes one of the remarkable facts in medical history.

Up to the present time, it has almost universally been presumed that some combination or variation of the classic symptoms of pain, shock, dyspnea and cardiac failure is present in each case of myocardial infarction in which a considerable portion of the myocardium is involved.[3] The symptom of pain in myocardial infarction is conceded to be extremely protean and may encompass such locations as the chest, extremities, abdomen, neck or back. The subjective description of the pain is likewise varied, running the gamut from negligible discomfort to viselike agony, attended with a sense of doom. More recently the occurrence of myocardial infarction associated with classic symptoms other than pain has come to be stressed in the literature.

In the late 1920's a series of papers was published describing a syndrome of myocardial infarction without pain. In the cases reported, however, severe dyspnea was the presenting complaint frequently associated with cardiac failure. East, Bain and Cary,[4] in 1928, described

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1. Bonetus, cited by White, P. D.: Heart Disease, ed. 3, New York, The MacMillan Company, 1944.

2. Herrick, J. B.: Clinical Features of Sudden Obstruction of the Coronary Arteries, J. A. M. A. **59**:2015-2020 (Dec. 7) 1912.

3. Levine, S. A.: Coronary Thrombosis: Its Various Clinical Features, Medicine **8**:245-418, 1929. Kahn, M. H.: Prodromal Symptoms in Angina Pectoris, Am. J. M. Sc. **172**:418-425, 1926.

4. East, C. F. T.; Bain, C. W. C., and Cary, F. L.: Cardiac Infarction Without Pain: Series of Eight Cases, Lancet **2**:60-63, 1928.

5 cases with no pain but with severe dyspnea; associated cardiac failure occurred in 6. In 6 cases the diagnosis of infarction was confirmed by autopsy. Parkinson and Bedford,[5] in the same year, described 2 similar instances in a series of 100 cases of infarction. In 1932 Davis,[6] in a paper on this syndrome, advanced the theory that previous ischemia and fibrosis of the muscle might make it insensitive to pain. Stenn,[7] in 1935, and Smith and Brink,[8] in 1936, described similar cases. Bean,[9] in 1938, observed that pain was present in the acute episode in no more than 72 per cent of 1,287 cases of myocardial infarction. Master and others,[10] in a series of papers in the early 1940's, made a differentiation between acute coronary occlusion and acute coronary insufficiency. In the latter, infarction may occur without definite occlusion, such areas are usually small or minute, and there is less likelihood of such severe symptoms, including pain. This explanation for the occurrence of the relatively less severe symptoms associated with recurring ischemia is basically in agreement with that of Davis [6] for the cases without pain.

It is our impression from the study of a large series of autopsies in correlation with clinical histories that myocardial infarcts of considerable size are not infrequently appreciably older than any referable symptom. For example, an infarct obviously over six weeks old might be noted at autopsy, whereas symptoms might have been present for only one week. In addition, not only were symptoms frequently mild and atypical, but occasionally no symptoms referable to the cardiovascular

5. Parkinson, J., and Bedford, D. E.: Cardiac Infarction and Coronary Thrombosis, Lancet **1**:4-11, 1928.

6. Davis, N. S., III: Coronary Thrombosis Without Pain: Its Incidence and Pathology, J. A. M. A. **98**:1806 (May 21) 1932.

7. Stenn, F.: Painless Coronary Occlusion, Illinois M. J. **67**:381-382, 1935.

8. Smith, H. L., and Brink, J. R.: Acute Coronary Thrombosis Without Characteristic Pain and Without Symptoms of Shock: Report of Three Cases, Minnesota Med. **19**:346-349, 1936.

9. Bean, W. B.: Infarction of Heart: Symptomatology of Acute Attack, Ann. Int. Med. **11**:2086-2108, 1938.

10. Master, A. M.: Progress in Acute Coronary Artery Diseases: Acute Coronary Artery Insufficiency With and Without Acute Occlusion, New York Med. (no. 9) **2**:19-22, 1946; Relation of Effort to Acute Attacks of Myocardial Infarction, J. A. M. A. **129**:90-91 (Sept. 1) 1945. Master, A. M.; Jaffe, H. L.; Dack, S., and Grishman, A.: Coronary Occlusion, Coronary Insufficiency, and Angina Pectoris: Clinical and Post-Mortem Study, Am. Heart J. **27**:803-816, 1944. Master, A. M.: Coronary Heart Disease: Angina Pectoris, Acute Coronary Insufficiency and Coronary Occlusion, Ann. Int. Med. **20**:661-674, 1944. Master, A. M.; Dack, S., and Jaffe, H. L.: Follow-Up Studies in Coronary Artery Occlusion: Degree of Recovery, Symptoms, and Physical Signs, New York State J. Med. **42**:413-420, 1942; Premonitory Symptoms of Acute Coronary Occlusion: Study of Two Hundred and Sixty Cases, Ann. Int. Med. **14**:1155-1165, 1941.

system were present at all. A review of the literature revealed a remarkable paucity of material on the subject. A paper by Blumgart and others,[11] in which appeared a description of a case of massive infarction unassociated with other symptoms, was the only reference available. We therefore felt it pertinent to undertake a study of the relation between autopsy findings and the presence or absence of clinical symptoms in a large series of cases of proved myocardial infarction.

MATERIAL AND METHODS

The material for study was drawn from the records of a large general hospital, the only such city hospital serving a borough of 1,500,000 people in the city of New York. A review was made of all autopsies performed from January 1944 to March 1948. A total of 255 cases of myocardial infarction, in which diagnosis had been proved by gross and microscopic examination of necropsy material, had been recorded during the period. The clinical histories in all cases were carefully reviewed; a history was regarded as containing proof of symptoms of cardiac disease when the following indications were noted, singly or in any combination: (1) pain in any of the accepted locations; (2) shock not obviously due to other causes; (3) dyspnea, and (4) myocardial failure, regardless of cause. All cases in which the history was deemed inadequate for this survey for any cause were arbitrarily rejected; only cases in which a definite negative statement appeared in the record in regard to the symptoms of interest were accepted as asymptomatic. We believe that the histories thus obtained constitute as accurate a group as can be gathered in such a study. The myocardial infarcts in the pathologic material used in this study were all dated as to approximate age. We wish to emphasize that the basic pathologic material used in this study was that of myocardial infarction and that material indicating occlusion of the coronary vessels, while included, was of secondary consideration. The reasons for this procedure were that infarction is a definitely recognizable pathologic entity and that occlusion of the smaller branches could easily have been overlooked when present without demonstrable infarction, since the technic of injection of the coronary vessels was not used.

Three categories of cases were accepted as meeting our criteria: (1) Cases in which infarcts were associated with negative histories of symptoms of cardiac disease, as determined by the method described (cases in this category were classified in three groups, [*a*] those in which the infarcts were fresh, [*b*] those in which the infarcts were old and [*c*] those in which multiple infarcts were present, both fresh and old); (2) cases in which symptoms of cardiac disease were present, but in which the infarcts obviously were older than the symptoms by an appreciable interval of time, and (3) cases in which a fresh infarct was attended by symptoms, but in which an older infarct was also present, unassociated with any corresponding symptoms of cardiac disease.

The classification of the infarcts as to age requires explanation. One of us (A.A.) has been directing his attention to this problem for many years. The experimental data obtained from dogs for judging the time factor as related to the secondary

11. Blumgart, H. L.; Schlesinger, M. J., and Davis, D.: Studies on the Relation of the Clinical Manifestations of Angina Pectoris, Coronary Thrombosis, and Myocardial Infarction to the Pathologic Findings, with Particular Reference to the Significance of Collateral Circulation, Am. Heart J. **19**:1-91, 1940.

changes in infarcted muscle does not seem to permit of direct application to human material. There exists, in fact, a pronounced variation in the appearance of infarcts of corresponding age among different human beings. The appearance of infarcts of the same age varies with the extent, depth, size, degree of ischemia, state of collateral circulation, location of the zone of hemorrhage and congestion, previous fibrosis, presence of infarction or infection anywhere else in the body and many other factors. However, it is obvious that an infarct which shows a sharply defined zone of necrosis and a sharp limitation of the marginal zone of absorptive changes and congestion has required time to reach such a state. Pronounced regional inflammation with extensive fibroblastic invasion and absorptive changes in adjacent muscle observed on microscopic examination cannot be fresh in the sense of being only a few days old. Such changes require weeks to develop; if the zone of absorption is large, several months may have been necessary. It was only such obviously time-consuming reactive and absorptive changes which were used to classify infarcts as of weeks' and months' duration.

TABLE 1.—*Cause of Death in 42 Cases of Myocardial Infarction* *

Associated Condition	Total Number of Cases	Cases in Which Condition Other than Infarct Was Cause of Death	Cases in Which Infarct Was Cause of Death
Carcinoma	8	5	3
Gallbladder disease	6	0	3
Bronchopneumonia	5	4	1
Diabetes mellitus	4	2	1
Vascular thrombi	3	3	0
Adenomas of the thyroid	1	0	1
Diverticulitis	1	1	0
Pyelonephritis	1	0	0
Infection with Bacillus welchii	1	1	0
Fracture of the femur	1	0	1
Herpes zoster	1	0	0
Berry aneurysm	1	1	0
Tuberculosis of the kidney	1	0	1
Meckel's diverticulitis	1	0	1
Nephrosclerosis	1	0	1
Laennec's cirrhosis	1	1	0
Encephalomalacia	1	0	0
Varicose ulcers (Ulcus hypostaticum)	1	0	1
Femoral hernia	1	0	1
Internal cecal hernia with peritonitis	1	1	1
Cystitis	1	0	0

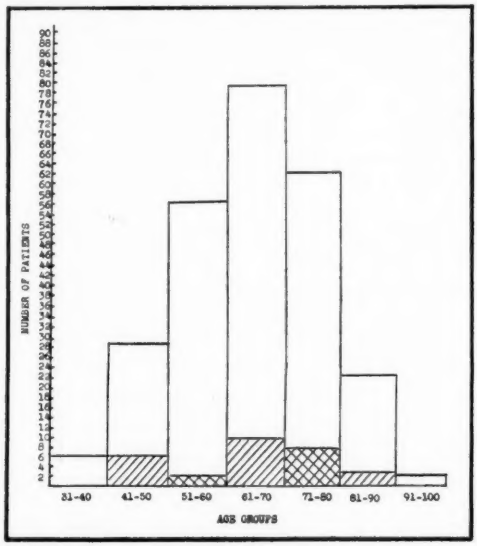
* In 1 case a fresh occlusion without infarction was the cause of death, and in 1 case a fresh occlusion without infarction and associated bronchopneumonia was the cause of death.

RESULTS

Of the 255 cases of myocardial infarction, 28, or 11 per cent, met the criteria of absence of all the factors of pain, shock, dyspnea and congestive failure. The group consisted of 4 cases with single fresh infarcts, 11 cases with multiple fresh and old infarcts and 13 cases with old infarcts.

Of the 255 patients, 161 were male and 94 female. Of the 28 asymptomatic patients, 16 were male and 12 were female. In the total series there was a somewhat larger percentage of female patients than is generally the case; the ratio of male patients to female patients in the asymptomatic group was not significantly different. It is of interest

that gallbladder disease or diabetes mellitus, or both, were present in 6 of the 12 asymptomatic female patients. These conditions are considered by many to predispose to coronary disease (table 1). A formal study in this regard made in the same service on similar material showed no significant correlation between the incidence of gallbladder disease and that of coronary sclerosis.[12] In the entire series, 248 patients were white and 7 were Negroes, whereas in the asymptomatic group all 28 patients were white.



Age distribution of patients with myocardial infarction. Shaded areas represent patients with asymptomatic infarcts.

The age distribution in the total group as compared with that in the asymptomatic group can be seen in the chart; it was approximately the same for the two groups. A correlation of the weights of the hearts in the two groups revealed nothing significant.

As described previously, all 28 cases in the asymptomatic group were classified in one of three categories. Nineteen cases were classified in the first category, in which infarcts were associated with negative

12. Russo, C., and Angrist, A.: Five Years of Gallbladder Disease at Autopsy in a General Hospital: Review of 2,450 Consecutive Routine Autopsies, Am. J. Surg. **58**:398-403, 1942.

histories of symptoms of cardiac disease; 3 of these cases in which the infarcts were fresh were classified in group *a*. The following report is a summary of a typical case in this group:

CASE 1.—B. K., a white woman of 68, was admitted with the chief symptom that of hematemesis of one day's duration. She had vomited black material three times. Dark stools had been present for several days. Discomfort after the ingestion of fatty foods had been noted for several months. No cardiac pain had ever been present. The patient denied a history of alcoholism. She had an episode of mild congestive failure one year before admission; the condition had been treated with digitalis for one month, and the patient had no further symptoms of this nature. Physical examination revealed a well developed, well nourished, extremely pale white woman with a blood pressure of 104 systolic and 60 diastolic, pulse rate of 130 and temperature of 100.4 F. The significant findings were enlargement of the heart to the left, a loud mitral first sound, a soft precordial systolic murmur and an enlarged liver. The initial clinical impression was hematemesis, possibly secondary to Laennec's (portal) cirrhosis and bleeding esophageal varices. After a transfusion (hemiplegia right) developed. The patient's condition became rapidly worse, and she died two days after the transfusion. At necropsy the findings were Laennec's cirrhosis with bleeding esophageal varices, hemorrhagic softening of the left cerebral cortex and a recent hemorrhagic infarction in the interventricular septum of moderate size and two or three days old. The coronary vessels were moderately sclerotic, but no gross occlusions were present.

The previous case was one in which the hemorrhage and resulting anoxia may well have precipitated the infarction in the myocardium which corresponded to the initial bleeding three days before death. None of the symptoms in the case was referable to the infarction.

Ten cases in which the infarcts were old were classified in group *b*. The following summary is that of a typical case:

CASE 2.—J. F., a 57 year old white man, was admitted to the hospital for the second time for weakness and dyspnea; one month before he had been hospitalized for cough, weakness and easy fatigue. The condition had been diagnosed as minimal pulmonary tuberculosis. Between admissions he had shown loss in weight of 3 or 4 pounds and a productive cough had developed. The patient stated that the respiratory difficulty had begun only a few days prior to the first admission. He denied the presence of edema of the ankles, palpitation or precordial pain. Physical examination on his second admission revealed a temperature of 100 F., a pulse rate of 100, a blood pressure of 126 systolic and 78 diastolic and a respiratory rate of 30 per minute. The patient was in acute asthmatic distress. The lungs were emphysematous, and the accessory respiratory muscles were being used. Scattered rhonchi and fine rales were present throughout the lungs. A pronounced decrease in breath sounds was present over the upper lobe of the left lung. Amphoric breath sounds were noted over the upper lobe of the right lung. The heart sounds were distant, but otherwise the cardiac findings were within normal limits. The rest of the physical examination was noncontributory. Bronchiectasis, pulmonary abscess, tuberculosis and bronchiogenic carcinoma were considered in the differential diagnosis. A roentgenogram of the chest reevealed an infiltration in the upper lobe of the right lung, which was unchanged since the first admission. In the hospital the course of the patient's illness was

downhill, and he died five days after admission. Autopsy revealed acute and chronic purulent bronchitis and bronchiectasis with emphysema. A bronchopneumonia was present in the upper lobe of the right lung, and both upper lobes showed pulmonary fibrosis. Minimal cor pulmonale was present. A large myocardial infarct with pronounced fibrous replacement, at least several months old, involved the entire wall of the left ventricle and the interventricular septum. Moderate nephrosclerosis and minimal hypertrophic gastritis were incidental findings.

Terminal symptoms in this case were definitely related to the pathologic condition in the lungs. The history of symptoms was unrelated to the old fibrotic infarct, which long antedated the pulmonary disease. No fresh lesion was observed anywhere in the myocardium.

Case 3 is typical of the 6 cases classified in group *c*, in which multiple infarcts, both fresh and old, were present.

CASE 3.—E. O., a white woman of 48, had been well until one day before admission, when pain in the back of the head, stiff neck and weakness suddenly developed. The history was noncontributory except for known hypertension of two years' duration and a cesarean section sixteen years before admission. Physical examination revealed a well developed, well nourished white woman, extremely lethargic but able to respond to questions and direction. The blood pressure was 150 systolic and 90 diastolic. The pulse rate varied between 72 and 120. The temperature was 100.4 F. Significant findings were ptosis of the right eyelid, rolling of the eyes, dilatation of the right pupil, weakness of the right side of the face and protrusion of the tongue to the right. The neck was stiff. The upper left extremity seemed weaker than the right. The spinal fluid was xanthochromic. The initial clinical impression was ruptured "Berry" aneurysm with subarachnoid hemorrhage. The patient soon lapsed into coma and died. The autopsy findings were a "Berry" aneurysm of the right superior cerebellar artery with rupture and subarachnoid hemorrhage, an old fibrotic infarct in the interventricular septum and a fresh hemorrhagic infarct in the posterior wall of the left ventricle, with a corresponding fresh occlusion in the posterior descending branch of the right coronary artery.

In this case neither the old infarct nor the fresh one was attended with any corresponding symptoms.

In the second category were the cases of infarction in which the duration of the symptoms did not correspond at all to the age of the infarct found at autopsy; in these 3 cases the infarct obviously antedated the appearance of symptoms. This fact would imply that the original infarct was asymptomatic. Not uncommonly, an infarct of six or eight weeks' duration is encountered at autopsy in a case in which the symptoms date back only a few days. Symptoms in such cases may be of a dramatic nature, including collapse and pain, but are not preceded by symptoms corresponding to the actual age of the necrotic process in the muscle and its subsequent organization, absorption and inflammation. Such cases are often recorded in medical examiners' or coroners' files as cases of sudden death with no previous medical attention, evi-

dence of preceding illness or symptoms. This large and important group is, of course, not represented in the present material.

A typical case in the second category is summarized.

CASE 4.—E. L., a white woman of 79, was admitted to the hospital for progressive weakness and dizziness of three or four weeks' duration. On the day prior to admission she had become somewhat dyspneic. The past history was completely noncontributory: She had never had cough, pain in the chest, dyspnea, palpitations or edema of the ankles. Physical examination revealed a pulse rate of 86, a blood pressure of 128 systolic and 86 diastolic, a temperature of 98 F. and a respiratory rate of 16. The significant physical findings were bilateral senile cataract, deviation of the trachea to the right and moist and crepitant rales at the bases of both lungs. The cardiac findings were within normal limits. A questionable Babinski reflex was present on the right side. The clinical impression on her admission was cerebral thrombosis and arteriosclerotic heart disease. The patient was digitalized and seemed to be doing well, when she suddenly died four days after admission. Autopsy revealed a massive infarction, at least two weeks old, involving the interventricular septum and both ventricles. An organized thrombus was present in the left ventricle, overlying the infarct. There was a recent occlusion of the anterior descending branch of the left coronary artery. The pericardial sac contained some sanguineous fluid; confluent bronchopneumonia was also present. Multiple uterine fibroids and thyroid adenomas were incidental findings.

Asymptomatic old infarcts were present in the remaining 2 cases in this group. However, acute terminal symptoms in both these cases could be correlated with a fresh occlusion, observed at autopsy in one of the coronary vessels without corresponding infarction. It was felt that death ensued too soon in these 2 cases to allow for morphologic evidence of fresh infarction. In these 2 cases, of course, the old infarcts represented the asymptomatic lesions.

The third category included those cases in which a fresh infarct was attended with symptoms and in which an older infarct was also present, but was unassociated with any corresponding symptoms of cardiac disease. The following summary is typical of the 6 cases in this category:

CASE 5.—H. R., a white man of 43, on the day of admission had onset of severe, sharp pain in the chest, radiating to the back. Dyspnea developed several hours later. One week before admission the patient had first experienced slight pain in the chest on exertion, but he had had no previous symptoms of cardiac disease. There was a history of appendectomy at the age of 22 years. Physical examination showed a blood pressure of 148 systolic and 104 diastolic, a pulse of 136, a respiratory rate of 32 and a temperature of 99.6 F. The patient was anxious. The skin was clammy. The significant findings were slight enlargement of the heart and moist rales throughout both lungs. The initial diagnosis was acute coronary occlusion with myocardial infarction. The dyspnea increased, the blood pressure fell and the patient died two days after admission, despite all possible treatment. At autopsy a fresh infarct was observed in the posterior wall of the left ventricle, with a corresponding occlusion in the circumflex branch

of the left coronary artery. Two old infarcts were present, one in the anterior wall of the left ventricle and one in the interventricular septum. All the coronary vessels were extremely sclerotic, but no other occlusions were present.

The old fibrotic infarcts obviously antedated the symptoms in this case.

The positions of the infarcts in the 28 cases corresponded fairly well with those usually described in the literature.[18] The three commonest sites were the anterior wall alone (6 cases), the anterior wall and the septum (7 cases) and the septum alone (7 cases). The posterior wall (5 cases) and the posterior wall and the septum (2 cases) were less frequently involved. The locations of occlusions of the coronary vessels also paralleled fairly well those described in the literature. The anterior descending branch of the left coronary artery was most frequently involved (12 cases); the right coronary artery was involved in 4 cases,

TABLE 2.—*Occlusion in 28 Cases of Asymptomatic Infarction*

Infarcts	Cases Without Occlusion	Cases With Single Occlusion		Cases With Multiple Occlusions			Number of Infarcts		
		Fresh	Old	Old	Fresh	Fresh and Old	Total	Terminal	Non-terminal
Single									
Fresh	2	2	0	0	0	0	4	1	3
Old	4	2	4	0	0	0	10	0	10
Multiple									
Old	0	1	0	0	0	2	3	0	3
Fresh and Old	3	4	2	0	0	2	11	8	3
Totals	9	9	6	0	0	4	28	9	19

and the circumflex branch of the left coronary artery, in 5. The relation of number to age of infarcts and occlusions may be seen in table 2. The last two columns in this table show whether or not the infarcts were the cause of death. Table 1 indicates all the associated conditions in these cases and the cause or causes of death. All infarcts in these cases, regardless of whether they were the cause of death, were of considerable size and did not represent merely changes due to insufficiency or mottling, requiring confirmation by microscopic studies. Necrotic muscle or a wide zone of scarred muscle was grossly obvious in all cases.

A varied amount of associated cardiac pathologic change was found in the 28 cases. In 16 cases some degree of hypertrophy and dilatation of the heart was present. Aneurysmal dilatation of either the septum or the wall of the left ventricle was present in 4. In 3 cases there were

13. White, P. D.: Heart Disease, ed. 3, New York, The Macmillan Company, 1944.

adherent mural thrombi in the atriums or ventricles. In 1 case each there was syphilitic aortitis, acute myocarditis, acute cor pulmonale, tuberculous pericarditis, old rheumatic endocarditis, recent thrombotic nonbacterial endocarditis, subendocardial hemorrhage and perforation of the pulmonary valve. In only 3 of the cases were mural thrombi present. This is a far smaller percentage than that usually reported in the literature.

The pericardium was recorded as showing inflammation or effusion, or both, in 13 cases. While pericardial involvement is frequently cited as a cause of precordial pain, this was obviously not the situation in the 13 asymptomatic cases.

The number of cases of hypertension could not be determined because the blood pressure previous to admission was unknown in most instances. Since the recorded blood pressure could have been lowered because of infarction or any of the associated conditions, it cannot be used as an index of hypertension.

COMMENT

We wish to stress that we are presenting the problem of asymptomatic infarction, and not that of occlusion of the coronary vessels. The better the syndrome of myocardial infarction has come to be understood through the years, the more varied the clinical picture has been found to be. It has been recognized that the symptoms in this condition may vary from the ultimate of sudden death to an atypical mild picture. It is now apparent, from the absence in this study of the correlation ordinarily encountered between the age of the infarct as observed at autopsy and the date of onset of clinical symptoms and signs, that large myocardial infarcts may occur frequently with none of the symptoms that are commonly expected (table 3). Although not shown in this paper because of the difficulty in obtaining clearcut material, the impression persists that in many ordinary cases with definite acute symptoms, the presence of the infarct antedates the exact time of onset of the clinical picture by an appreciable interval.

Before we undertook this study, it was our impression that the asymptomatic syndrome occurred predominantly in the aged. However, because of our rigid criteria, we were compelled to exclude many cases which probably represented actual asymptomatic infarcts. For example, several cases of pulmonary tuberculosis with long-standing dyspnea and several cases of long-standing, mild congestive failure in aged people had to be excluded.

Many standard forms of treatment are subject to analysis on the basis of the results of this study. The absence of symptoms and the existence of an asymptomatic period in cases of myocardial infarction

are of major significance and prompt a review of the entire problem of diagnosis, prognosis and treatment in its relation to the dating of the exact onset of the necrotic changes in the cardiac muscle. Should one prescribe the traditional six to eight week period of rest in bed for a patient whose infarct is already a month old? Should one administer heparin and dicumarol® when the occlusion of the coronary artery and any overlying mural thrombus may already have undergone partial organization? Can dicumarol® or heparin be effective except

TABLE 3.—*Symptoms in 28 Cases of Myocardial Infarction*

Patient	Number of Infarcts			Symptoms
	Total	Fresh	Old	
H. R.	3	1	2	Only symptoms ten days before admission
M. H.	1	0	1	None
E. L.	1	1	0	One day of dyspnea
E. O.	2	1	1	None
C. S.	2	1	1	One week of dyspnea
J. Y.	1	0	1	None
G. K.	2	1	1	None
M. R.	2	1	1	None
W. P.	1	0	1	None
J. S.	2	0	2	Acute decompensation
L. C.	1	1	0	None
V. K.	1	0	1	None
M. M.	2	1	1	Acute precordial pain and dyspnea
S. P.	2	0	2	None
J. H.	1	0	1	None
A. H.	1	0	1	None
K. S.	2	1	1	None
O. L.	1	0	1	Recent pain in chest (carcinoma of the lung)
J. M.	1	0	1	None
B. K.	1	1	0	None
S. F.	2	0	2	None
M. V.	2	1	1	Recent sudden pain and dyspnea
H. J.	1	0	1	Terminal dyspnea
J. M.	1	0	1	None
J. B.	several	several	several	None
W. M.	1	1	0	None
B. B.	2	1	1	None
C. S.	2	1	1	Nine hours of dyspnea and pain

in the early stages of thrombosis of the coronary vessels? How effective can these drugs be if there exists the difficulty of dating infarcts according to symptoms?

In differential diagnosis, the existence of asymptomatic infarcts becomes a consideration in any case of an obscure condition in a patient of the usual age group. Particularly in aged patients who fail to respond after operation, or who fail to respond to a treatment usually favorable for a certain medical condition, the presence of asymptomatic myocardial infarction must be suspected. Sudden cerebral insufficiency in aged persons or sudden failure in any case, with or without shock, is often explained by such infarction.

Dramatic or recurrent clinical episodes in cases of myocardial infarction may represent symptomatic episodes on a purely functional basis. We wish to stress the implication that functional alterations, not directly dependent on the existence of necrotic muscle as such, may be the significant factor in determining the clinical syndrome during life, just as they are so often the fundamental basis for the understanding of the cause of death in cases of this syndrome.

SUMMARY AND CONCLUSIONS

Of 255 cases of myocardial infarction in which the diagnosis was verified by autopsy at a large general hospital in New York, no corresponding history or other evidence of symptoms of cardiac disease was present in 28.

Attempted correlations in regard to age, sex, race and size of heart between the asymptomatic group and the entire group revealed nothing significant.

The asymptomatic cases were classified in categories; summaries of typical cases are presented.

The positions of the infarcts and occlusions in the asymptomatic cases were not significantly different from those described in the literature.

A discussion of the associated conditions in the asymptomatic group is presented.

Certain recognized concepts in diagnosis, prognosis and treatment of the clinical syndrome of myocardial infarction are questioned in the light of the findings.

The concept is presented that clinical episodes in cases of myocardial infarction may frequently represent symptomatic episodes on a purely functional basis.

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Progress in Internal Medicine

GASTROENTEROLOGY

A Review of the Literature from July 1947 to July 1948

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From the University of Chicago, The School of Medicine.

GASTRIC NEOPLASMS

Polyps and Benign Tumors.—Carey and Hay [242] review a series of 71 cases of gastric polyps, in which the lesions were seen at gastroscopic examination. The lesion in 5 cases proved to be malignant; no free acid was demonstrated after histamine stimulation; the mucosa appeared atrophic in 4 and polypoid in 1. Among the remaining 66 cases, the mucosa was atrophic in 46, normal in 11 and hypertrophic in 9. Free acid was present in the gastric content in 13; achlorhydria was noted after administration of histamine in 46 and after a test meal in 6; in 1 the acidity was not measured. Among the 68 cases in which roentgenologic examination was made, polyps were identified in 30 and were not seen in 38. Polyps in 3 of 23 cases described by Moutier and Cornet [243] proved to be malignant. Bruskin [244] recommends gastric resection in cases of polyps because of the tendency to neoplasia. Benign tumors are discussed also by Baravalli,[245] Ikle,[246] Pevaroff,[247] and Señorans and his associates.[248]

Leiomyoma.—Kirshen, Weinberg and Cohen [249] describe a case in which a leiomyoma was located near the cardia. The symptoms were those of intermittent hemorrhage and pain; a combined roentgenologic and gastroscopic study permitted the diagnosis. The lesion was removed surgically, with complete clinical cure. An unusual leiomyoma is reported by Moulonguet.[250]

Leiomyosarcoma.—The body of a woman of 59, who had died of severe hemorrhage, was found at autopsy to contain a large leiomyosarcoma of the stomach, with metastases to the liver. The histologic appearance of the lesion was bizarre, with spindle-shaped nuclei, whorl-

242. Carey, J. B., and Hay, L.: Gastric Polyps, Gastroenterology **10**:102, 1948.

243. Moutier, F., and Cornet, A.: Tumeurs benignes de l'estomac, Semaine d. hop., Paris **23**:1343, 1947.

244. Bruskin, Y. M.: Polyps and Polypous Gastritis as Precancerous Conditions of the Stomach, Khirurgiya **9**:70, 1947.

245. Baravalli, N.: Benign Tumors of the Stomach, An. de cir. **12**:221, 1947.

246. Ikle, A.: Clinical and Pathological Studies of Papillary Mucosal Tumors of the Stomach: Gastric Papillomas, Helvet. chir. acta **14**:435, 1947.

247. Pevaroff, H. H.: Benign Tumors of the Stomach, Am. J. Surg. **74**:488, 1947.

248. Señorans, A. J.; Bustos Fernández L., and Covelli, R.: Tumors benignos de estómogo: Tres observaciones, Arch. argent. de enferm. d. ap. digest. de la nutrición **22**:31, 1947.

249. Kirshen, M. M.; Weinberg, B. J., and Cohen, A.: Leiomyoma of the Stomach, Gastroenterology **9**:466, 1947.

250. Moulonguet, M. P.: Formes localises de l'hypertrophie musculaire du pylore, Arch. d. mal. d. l'app. digestif **36**:499, 1947.

ing of the cells, pseudorosette formation, irregularity of the size of the nuclei and degenerative changes in different locations.[251]

Shallenberger and Doane[252] describe 2 cases of leiomyosarcoma in 1 of which the diagnosis was made before operation. In 2 cases, Palmer[253] noted "malignant intramural infiltration with prominent smooth, non-ulcerated, hemispheric nodules, and increased translucency of the overlying mucosa" at gastroscopic examination. A leiomyosarcoma was removed successfully through a thoracicoabdominal incision.[254]

Sarcoma and Lymphosarcoma.—Nineteen cases of sarcoma are reviewed by Spencer and Collins.[255] Successful resection is reported in 2 cases.[256] Renshaw and Spencer[257] describe the appearance of the stomach at gastroscopic examination in cases of lymphomatous diseases. No characteristic picture was observed; at gastroscopic examination the lesion usually is indistinguishable from a carcinoma. O'Donoghue and Jacobs[258] collected reports of 100 cases of primary lymphosarcoma from the literature and describe a patient who was alive and well five and one-half years after resection. Reports of other interesting cases are published.[259]

A patient with reticulum cell sarcoma of the stomach was alive one year after gastric resection.[260] Hodgkin's disease of the stomach is reported.[261] Three papers deal with schwannoma.[262]

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251. McNeil, C., and Hesse, F. E.: Pathologic Aspects of Leiomyosarcoma of the Stomach, Arch. Path. **44**:138 (Aug.) 1947.

252. Shallenberger, P. L., and Doane, J. H.: Leiomyosarcoma of the Stomach, Guthrie Clin. Bull. **17**:59, 1947.

253. Palmer, E. D.: Leiomyosarcoma of the Stomach with Particular Reference to the Gastroscopic Picture, Am. J. Digest. Dis. **15**:84, 1948.

254. Forty, F.: Leiomyosarcoma of the Stomach: Thoracico-Abdominal Gastrectomy, Proc. Roy. Soc. Med. **41**:100, 1948.

255. Spencer, F. M., and Collins, E. N.: Sarcoma of the Stomach, Cleveland Clin. Quart. **14**:282, 1947.

256. Crousse, R., and DeWitte, J.: Sarcomes primitifs de l'estomac, Acta gastroenterol. belg. **11**:23, 1948.

257. Renshaw, J. J., and Spencer, F. M.: Gastroscopy and Lymphoma of the Stomach, Gastroenterology **9**:1, 1947.

258. O'Donoghue, J. B., and Jacobs, M. B.: Primary Lymphosarcoma of the Stomach, Am. J. Surg. **74**:174, 1947.

259. Berman, H.: Lymphosarcoma of the Stomach, M. Rec. **160**:30, 1947. Morgans, M. E.; Rimington, C., and Whittaker, N.: Folic Acid in Megaloblastic Anæmia After Total Gastrectomy, Lancet **2**:128, 1947.

260. Dubost, C.: Sur un cas de reticulose histio-monocytaire tumorale a localization gastrique, Presse méd. **56**:456, 1948.

261. Farneti, F.: Linfogranulomation isolata e primitoa dello stomacs, Arch. ital. mal. app. diger. **13**:2, 1947.

262. Gomez, J.: Schwannoma of the Stomach (Based on Four Cases), J. de chir. **63**:463, 1947. Prat, D., and Ardao, H.: Schwannoma of the Stomach, Arch. urug. de med., cir. y especialid. **30**:379, 1947. Cornil, L., and Gastaut, H.: Memmoschwannoblastoma de l'estomac, Bull. Assoc. franç. p. l'étude due cancer **34**:43, 1947.

Neurogenic Tumors.—Other unusual tumors include neuroepithelioma,[263] neurofibroma[264] and neurilemmoma.[265] West and Knox[266] record 7 cases of neurogenic tumor and 1 of smooth muscular tumor; bleeding was the chief symptom in 6 cases.

Miscellaneous Tumors.—A young man, operated on for acute retention of urine, was found to have an endothelioma growing in the greater omentum which had ulcerated into the gastric lumen and was impacted in the pelvis in such a way as to press on the lower end of the bladder and ureters. Excision of the mass with a cuff of stomach was successful; the patient was symptom free four years later.[267] Other rare gastric tumors are carcinoid,[268] myxoma[269] and myxofibroma.[270]

GASTRIC CANCER

General Survey.—Problems in diagnosis, the low five year survival rate, methods of achieving earlier diagnosis and improvement in treatment are discussed in numerous papers.[271] As in the past, emphasis is directed to the need for constant awareness of the possible presence of a malignant lesion, frequent roentgenologic and gastroscopic examinations, and operation in the presence of suspicious symptoms. Increased publicity, education of the public and the establishment of centers for the

263. Gillespie, H. W.: Neuroepithelioma of the Stomach, Brit. J. Radiol. **20**:433, 1947.

264. Tate, R. W., and Fusuro, W. J.: Neurofibroma of the Stomach, Am. J. Surg. **75**:607, 1948.

265. Byers, R. S., and Howard, J. W.: Gastric Neurilemmoma: Report of Four Cases, Delaware State M. J. **20**:1, 1948.

266. West, J. P., and Knox, G.: Neurogenic Tumors of the Stomach, Surgery **23**:450, 1948.

267. Guthkelch, A. N.: Endothelioma of the Stomach Causing Acute Retention of Urine, Brit. J. Surg. **35**:439, 1948.

268. Gallinaro, A. E.: Leso carcinoidas de l'estomac, Arch. ital. chir. **69**:239, 1947.

269. Señorans, A.; Siccardi, B., and Lascano, E.: Mixoma gástrico, Arch. argent. de enferm. d. ap. digest. y de la nutrición **22**:86, 1947.

270. Galletti, G.: Su un caso di fibroma mixomatode dello stomacs con speriale sigmardo all'istogenin della sostanza mucoide interfibrillase, Arch. ital. mal. app. diger. **14**:29, 1948.

271. (*a*) Ogilvie, H.: The Early Diagnosis of Cancer of the Esophagus and Stomach, Brit. M. J. **2**:405, 1947. (*b*) Stout, A. P.: Tumors of the Stomach, Bull. New York Acad. Med. **23**:101, 1947. (*c*) Shorter, A.: The Problem of Gastric Cancer, Lancet **2**:842, 1947. (*d*) Wangensteen, O. H.: The Problem of Gastric Cancer, J. A. M. A. **134**:1161 (Aug. 2) 1947. (*e*) Taylor, H.: Carcinoma of the Stomach, Lancet **1**:581, 1948. (*f*) Jennings, D.: The Statistical Approach to Gastric Cancer, Brit. J. Radiol. **20**:522, 1947. (*g*) Grout, J. L. A.; Rodgers, H. W.; Stewart, M.; Taylor, H.; Fairchild, G. C., and Jennings, D.: Carcinoma of the Stomach: Symposium, Brit. J. Radiol. **20**:491, 1947. (*h*) Pack, G. T., and McNeer, G.: The Incidence of Gastric Cancer, Internat. Abstr. Surg. **86**:521; in Surg., Gynec. & Obst., June 1948. (*i*) Engel, G. C.: Reducing Mortality in Gastric Carcinoma, J. A. M. A. **135**:687 (Nov. 15) 1947. (*j*) Welch, C. E., and Allen, A. W.: Carcinoma of the Stomach, New England J. Med. **238**:583, 1948.

detection of cancer are advocated by Shorter,[271c] Wangensteen,[271d] Taylor,[271e] and others. The reviewers are in accord with the suggestions but are not optimistic that they will solve the problem.

Welch and Allen,[271j] in a review of the cases of all patients with carcinoma of the stomach admitted to the Massachusetts General Hospital during the decade from 1937 to 1946, found that the average delay before treatment had remained at five months. The rates of operability and resectability had increased, whereas the mortality rate had decreased. The five year survival rate for the entire group was 7 per cent.

In a mass survey by Swenson [272] of 2,500 patients aged 50 or more and examined by a rapid fluoroscopic technic, early, asymptomatic carcinoma of the stomach was found in 3 instances; surgical exploration was warranted in 5. The importance of periodic roentgenologic and gastroscopic studies in all cases of Addison's anemia (pernicious anemia) is again indicated by the discovery of gastric cancer in 3 of 15 cases of pernicious anemia in which the patients were free of digestive symptoms.[273] Examination of patients with idiopathic atrophy of the gastric mucosa, as well as of persons with pernicious anemia, would appear to be a fruitful study.

Roentgenologic Aspects.—The roentgenologic features of gastric cancer and the difficulties in diagnosis are emphasized by Grant,[274] Sherman,[275] Geuens,[276] Crismer,[277] and Albot and his co-workers.[278]

Schindler,[279] with characteristic thoroughness, describes the differentiation between benign and malignant gastric ulcers at gastroscopic examination, emphasizes the importance of the examination and concludes that, though not infallible, it is the most important method for the differential diagnosis.

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272. Swenson, P. C.: Mass Survey of the Gastrointestinal Tract, South. M. J. **41**:108, 1948.

273. Bourne, W. A.: Cancer of the Stomach in Addison's Anemia, Brit. M. J. **1**:92, 1948.

274. Grant, J. L. A.: Carcinoma of the Stomach: A Radiologist's Point of View, Brit. J. Radiol. **20**:491, 1947.

275. Sherman, R. S.: The Roentgen Diagnosis of Cancer of the Cardiac Region of the Stomach, Surgery **23**:874, 1948.

276. Geuens, J.: Contribution à l'étude due diagnostic précoce du cancer gastrique, Acta gastroenterol. belg. **10**:402, 1947.

277. Crismer, R.: Le diagnostic radioclinique du cancer du pole supérieur de l'estomac et en particulier du cancer juxtacardiaque, Acta gastroenterol. belg. **11**:84, 1948.

278. Albot, G.; Garcia Calderon, G., and Marquis, G.: Pharmacodynamic Methods in Conjunction with Compression in Radiologic Diagnosis of Early Gastric Cancer, Arch. d. mal. de l'app. digestif **36**:277, 1947. Albot, G.; Toulet, J., and Libaude, H.: Diagnostic des niches en plateau, ibid. **37**:273, 1948.

279. Schindler, R.: Gastroscopic Differentiation of Benign and Malignant Ulcer, Gastroenterology **10**:234, 1948.

In a series of 131 cases in which operation was performed after a diagnosis of benign gastric ulcer, 26 lesions proved to be malignant, a diagnostic error of 19.8 per cent.[280] Malignant ulceration may occur anywhere in the stomach, but it is found most frequently in the prepyloric area, on the greater curvature and in the cardiac area; in cases of ulcers in these regions, resection should be done without delay. The authors state the belief that the treatment of gastric ulcer should be primarily surgical.

Cohn and Gold[281] report 8 cases of prepyloric spasm simulating a malignant growth at roentgenologic examination. Exploratory operation is indicated when the presence of a malignant lesion cannot be definitely excluded by all diagnostic aids. Abdominal exploration was carried out in 7 of 11 cases of prepyloric spasm[282] because of the difficulty in diagnosis; a slow-growing carcinoma of the pylorus was encountered in 1. Ulcerative gastritis with fibrosis of the prepyloric region simulated neoplastic infiltration.[283]

The difficulties in the differential diagnosis of various lesions of the pyloric antrum, including normal variations in the size of rugae, gastritis, benign hypertrophy of the pylorus, gastric ulcer, carcinoma, benign tumors, lymphosarcoma, syphilis and tuberculosis are reemphasized by Segal and his associates[284] and by Osgood.[285]

Pathologic Aspects.—The pathologic aspects of cancer of the stomach are discussed by Stewart.[286]

Cytologic Examination of Gastric Content.—Hunter,[287] Hartman,[288] and others[289] show that the cytologic examination of gastric content by

280. Marshall, S. F., and Welch, M. L.: Results of Surgical Treatment for Gastric Ulcer, J. A. M. A. **136**:748 (March 13) 1948.

281. Cohn, A. L., and Gold, R.: Prepyloric Spasm Simulating Gastric Malignancy, Gastroenterology **10**:782, 1948.

282. Tracey, M. L.: Habitual Prepyloric Spasm, S. Clin. North America **28**:777, 1948.

283. Crismer, R.: One Source of Error in the X-Ray Diagnosis of Gastric Cancer, Acta gastroenterol. belg. **10**:200, 1947.

284. Segal, H. L.; Watson, J. S., and Steinhausen, T. B.: Difficulties in the Diagnosis and Treatment of Lesions of the Pyloric Antrum, New York State J. Med. **47**:2292, 1947.

285. Osgood, H. A.: Diagnosis of Prepyloric Lesions in the Stomach, Rev. Gastroenterol. **15**:11, 1948.

286. Stewart, M. J.: Cancer of the Stomach: Some Pathological Considerations, Brit. J. Radiol. **20**:505, 1947.

287. Hunter, W. C.: Cytologic Recognition of Cancer in Expoliated Material from Various Sources, Surg., Gynec. & Obst. **85**:275, 1947.

288. Hartman, A. W.: The Problem of Early Diagnosis of Cancer of the Stomach, Texas State J. Med. **43**:637, 1948.

289. Campbell, J. P., and Grimm, H. A.: Experience with Papanicolaou Stains in the Study of Gastric Contents, Rev. Gastroenterol. **15**:21, 1948. Maggi, A. L. C., and Bonorino-Pero, C.: Exploración citológica del contenido gástrico, Arch. argent. de enferm. d. ap. digest. y de la nutrición **22**:184, 1947.

the method of Papanicolaou is of value in diagnosis. Graham, Ulfelder and Green [290] used the technic in 50 cases of gastric symptoms; diagnosis was correct in 15 of 24 cases of carcinoma and in 25 of 26 cases free of carcinoma. Among 7 cases of resectable carcinoma diagnosis was correct in 5.

Gastric Acidity.—In 277 cases in which gastric analysis was performed two or more years (mean interval, 11.2 years) before carcinoma was diagnosed, the mean secretory activity was subnormal. The evidence is interpreted as supporting the hypothesis that atrophy of the gastric mucosa is responsible for the depression of secretory activity before the development of carcinoma.[291]

Metabolic Changes.—Activity of the catalase and arginase in biopsy specimens from the liver of 16 patients with gastric cancer did not differ significantly from that in specimens from 11 patients with benign gastric lesions.[292] Male mice bearing implants of sarcoma 180 exhibited an impairment in the ability to store glycogen in the liver after the administration of glucose; a similar defect is observed in patients with gastric cancer.[293]

Superficial Spreading Carcinoma.—In a most interesting paper, Golden and Stout [294] review 31 cases of so-called superficial spreading carcinoma of the stomach; 21 were in men and 10, in women. One stomach contained two superficial spreading cancers; in 2 cases, mixed types of carcinoma were present. In 2 of the resected stomachs, multiple foci of superficial spreading cancer were found, with uninvolved mucous membrane between them. Metastases to regional lymph nodes were present in only 15 of the 31 cases. The superficial cancer developed in the lower half of the stomach in 30 of the 31 cases; in 1, it occurred around the cardiac orifice and involved the fundus. Gastroscopy was performed in 11 cases; in 9 the gastroscopist sooner or later found evi-

290. Graham, R. M.; Ulfelder, H., and Green, T. H., Jr.: The Cytologic Method as an Aid in the Diagnosis of Gastric Carcinoma, Surg., Gynec. & Obst. **86**:257, 1948.

291. Comfort, M. W.; Kelsey, M. P., and Berkson, J.: Gastric Acidity Before and After Development of Carcinoma of the Stomach, Proc. Staff Meet., Mayo Clin. **23**:135, 1948.

292. Young, N. F.; Collier, V., and Homburger, F.: Arginase and Catalase Activity in Livers of Patients Having Benign and Malignant Gastric Lesions, Proc. Soc. Exper. Biol. & Med. **66**:323, 1947.

293. Young, N. F.; Kensler, C. G.; Seki, L., and Homburger, F.: Deposition of Liver Glycogen in Normal Mice and in Mice Bearing Sarcoma 180, Proc. Soc. Exper. Biol. & Med. **66**:322, 1947.

294. Golden, R., and Stout, A. P.: Superficial Spreading Carcinoma of the Stomach, Am. J. Roentgenol. **59**:157, 1948.

dence interpreted as consistent with or suggestive of cancer. In 2 instances he saw no evidence of carcinoma. Superficial spreading carcinoma of the stomach grows along the mucosa or in the mucosa and submucosa. Its physical effects on the gastric wall are: (*a*) replacement of the mucosa; (*b*) radiation of the mucosal folds from the growth; (*c*) obliteration of the folds by the growth; (*d*) widening and stiffening of the folds immediately around the growth; (*e*) formation of nodules on the surface, and (*f*) ulceration. In the great majority of cases, the difficulty was not in the detection of abnormality on roentgenologic examination of the stomach, but rather, in making certain that cancer was or was not present in an obviously abnormal stomach. A case of superficial gastric cancer is described in a woman of 72 [295] and another, in a man of 31.[296]

Two cases of mucoid epithelioma of the stomach without ulceration or sclerosis are reported [297]; in both, operation eventually disclosed an extensive growth, although roentgen signs had been minimal. In the second case, although the results of gastroscopic examination indicated normalcy, the growth was found to involve almost the entire stomach three months later. Nevertheless, the authors consider gastroscopy the most important diagnostic method.

Unusual Cases.—Armstrong and Wilbur [298] describe 2 cases of a large malignant ulcer simulating diverticula. A man of 53 [299] presented subjective and objective signs of destruction of the sympathetic nerve chain on the right side between the first and the fourth thoracic segments. Almost two years later he complained of gas pains. A biopsy specimen taken from a mass over the rectus muscle proved the lesion to be an adenocarcinoma. At autopsy, a carcinoma of the stomach was found, with a metastatic lesion in the right costovertebral area at the fourth rib. In the case of a patient later found to have carcinoma,[300] the

295. Cattan, R.; Baumann, J.; Frumusan, F., and Attal, C.: A Case of Superficial Cancer of the Stomach, Arch. d. mal. de l'app. digestif **36**:295, 1947.

296. Hillemand, P.; Charrier, J.; Marre, P., and Toulet, J.: Cancer mucoérosif de l'estomac à marche lente, Bull. et mém. Soc. méd. de hôp. de Paris **64**:699, 1948.

297. Albot, G.; Marquis, G., and Tricard, A.: A Rare Anatomical and Radiological Form of Cancer of the Stomach Difficult to Diagnose and Its Early States: Mucoid Epithelioma Without Ulceration or Sclerosis, Arch. d. mal. de l'app. digestif **36**:238, 1947.

298. Armstrong, C. D., and Wilbur, D. L.: Malignant Disease of the Stomach Simulating Gastric Diverticulum, M. Clin. North America **32**:336, 1948.

299. Wikler, A.; Wiesel, C., and Maxwell, E. S.: Sympathetic Paralysis Due to Metastasis as Initial Sign of Gastric Carcinoma, Ann. Int. Med. **28**:648, 1948.

300. Baum, L. E.; Baum, O. S., and Hermann, J. H.: Thrombophlebitis Migrans in Carcinoma of the Stomach, J. M. Soc. New Jersey **45**:61, 1948.

primary clinical symptoms were those of migratory thrombophlebitis. Olenik [301] describes a subtotal resection, followed in seven months by local recurrence; a transthoracic resection of the remaining part of the stomach, splenectomy and partial pancreatectomy were then performed succesfully. A woman of 49 [302] with linitis plastica produced by a scirrhous carcinoma survived total gastrectomy; gastric symptoms had been present for approximately two years. Costello [303] reports a case of scirrhous carcinoma in which treatment was by subtotal gastrectomy; metastatic Krukenberg tumors of the ovaries subsequently were removed successfully. A similar sequence of events is described by Gutmann and others.[304] Dixon and Weismann [305] describe resection of a stomach containing three separate, sessile, ulcerating, carcinomatous masses.

Perforation is discussed by Forni.[306] Cancer of the subcardial region is considered in a well illustrated article by Moutier and Nemours.[307]

Carcinoma in Youth.—Twenty of 1,913 cases of gastric carcinoma (1+ per cent) reported during a twenty year period were in patients under 31 [308]; metastases were present in 17 at the time of initial examination. During the same period benign gastric ulcer was diagnosed in 50 cases in persons of the same age group, lymphoblastoma of the stomach in 2 and gastric syphilis in 1.

Surgical Treatment and Results.—Bell [309] states the belief that every patient with cancer of the stomach in whom the existence of distant metastases is not unequivocally proved should have an exploratory operation to determine whether or not the lesion is resectable. The reviewers are in accord with this view.

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301. Olenik, J. L.: Transthoracic Gastrectomy, Splenectomy, and Subtotal Pancreatectomy for Recurrent Carcinoma of the Stomach, New York State J. Med. **48**:1167, 1948.

302. Matzner, M. J.: Linitis Plastica with Total Gastrectomy, Rev. Gastroenterol. **14**:800, 1947.

303. Costello, R. C.: Carcinoma of the Stomach with Krukenberg Type of Ovarian Metastasis: Report of a Case, Ohio State M. J. **43**:941, 1947.

304. Gutmann, R. A.; Dupuy, R.; Carasso, and Gomez, M.: Un cas de cancer gastrique à évolution longue et larvée, Arch. d. mal. de l'app. digestif **37**:130, 1948.

305. Dixon, C. F., and Weismann, R. E.: Multiple Simultaneous Carcinomas of the Stomach Treated by Total Gastrectomy: Report of a Case, S. Clin. North America **27**:919, 1947.

306. Forni, G.: Acute Perforation of Gastric Carcinoma, Arch. ital. mal. app. diger. **14**:54, 1948.

307. Moutier, F., and Nemours, A.: Le cancer sus-cardial et juxta-oesophagien de la grosse tuberosite gastrique, Arch. d. mal. de l'app. digestif **37**:137, 1948.

308. Block, M.; Griep, A. H., and Pollard, H. M.: The Occurrence of Gastric Neoplasms in Youth, Am. J. M. Sc. **215**:398, 1948.

309. Bell, H. G.: The Problem of Gastric Cancer in a University Hospital, Surgery **23**:351, 1948.

Welch [310] states that patients with gastric ulcer should be subjected to immediate operation if any of the following conditions prevail: (*a*) the ulcer is of short duration and the patient is over 50; (*b*) the ulcer is on the greater curvature or in the prepyloric area; (*c*) the ulcer is 2.5 cm. or more in diameter; (*d*) there is no free hydrochloric acid in the stomach, or (*e*) the ulcer is chronic and on the lesser curvature. Gastric ulcer is regarded as fundamentally a surgical disease because of the difficulty in differentiation from cancer.

Smithwick [311] describes a closed (aseptic) method for esophagojejunostomy which may further reduce the operative mortality rate in total gastrectomy by minimizing the hazard of peritonitis due to local contamination. Two patients are reported living and well at the time of the report, five years two months and ten and one-half years, respectively, after total gastrectomy for carcinoma.

Priestley and Kumpuris [312] state that they prefer esophagoduodenal anastomosis to the more usual esophagojejunostomy. Total gastrectomy may be accomplished through the transthoracic or the combined thoracicoabdominal route.[313] Synchronous combined excision through thoracic and abdominal incisions by two surgeons is recommended by Hume and Blackburn.[314] The surgical aspects of carcinoma of the stomach are further discussed by many writers.[315]

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310. Welch, C. E.: Carcinoma of the Stomach, S. Clin. North America **27**:1100, 1947.

311. Smithwick, R. H.: Total Gastrectomy, with Particular Reference to Closed (Aseptic) Esophagojejunostomy, New England J. Med. **237**:39, 1947.

312. Priestley, J. T., and Kumpuris, F.: Total Gastrectomy with Esophagoduodenal Anastomosis, Arch. Surg. **56**:145 (Feb.) 1948.

313. Martinson, L. F.; Gillespie, S. R., and Hunter, A.: Transthoracic Gastrectomy, Northwest Med. **46**:685, 1947.

314. Hume, J. B., and Blackburn, G.: Synchronous Combined Total Gastrectomy, Brit. M. J. **2**:817, 1947.

315. (*a*) Taylor, H.: The Surgical Aspect of Carcinoma of the Stomach, Brit. J. Radiol. **20**:507, 1947. (*b*) Orban, F., and Dalem, J.: Traitement actuel des tumeurs du cardia, Acta gastroenterol. belg. **11**:94, 1948. (*c*) Landelius, E.: Results of Partial and Total Gastrectomy in Cancer of the Stomach, Acta chir. Scandinav. **96**:441, 1948. (*d*) Monteiro, A., and Barreto, H.: Aseptic Gastric Resection, Billroth I Technique, Surgery **23**:178, 1948. (*e*) Cooper, A. R., and Buxton, R. W.: Gastrostomy, ibid. **23**:821, 1948. (*f*) Ranson, H. K.: Total Gastrectomy, Ann. Surg. **55**:13, 1947. (*g*) State, D.; Moore, G., and Wangensteen, O. H.: Carcinoma of the Stomach, J. A. M. A. **135**:262 (Oct. 4) 1947. (*h*) Pack, G. T.; McNeer, G., and Booher, R. J.: Principles Governing Total Gastrectomy, Arch. Surg. **55**:457 (Oct.) 1947. (*i*) Lorange, M.: Gastric Cancer, Nord. med. **37**:171, 1948. (*j*) Nocito, F. J., and Coltini, G. F.: Cáncer de estómago, Prensa méd. argent. **34**:2228, 1947. (*k*) Feldman, M., and Morrison, S.: Cancer of the Stomach: A Statistical Study, South. M. J. **41**:567, 1948. (*l*) Lefevre, H.: La gastrectomie totale: Nouvelle technique operatoire; resultats, Rev. chir. **66**:148, 1947. (*m*) Pack, G. T., and McNeer, G.: Surgical Treatment of Cancers of the Gastric Cardia, Surgery **23**:976, 1948.

Ranson [315f] performed complete gastric resection by the abdominal route in the cases of 41 men and 19 women between the ages of 30 and 81. The original diagnoses were: carcinoma, 53 cases; gastric ulcer, 4; lymphosarcoma, 2, and neurofibroma, 1. There were 14 operative fatalities. The most frequent cause of death was generalized peritonitis; the source usually was leakage at the site of the esophagojejunal anastomosis. Among the 46 patients surviving the operation, 31 subsequently died owing to recurrence of the malignant disease. Three patients, after five year follow-up studies, were classified as cured. Those with benign lesions who survived operation were alive and in a satisfactory state of nutrition at the time of writing. In 2 patients, the classic picture of pernicious anemia developed approximately five years after operation; both patients responded to therapy with liver extract.

State, Moore and Wangensteen [315g] review the cases of 586 patients seen during the ten year period from 1936 to 1945. The rate of operability was 76.3 per cent; that of resectability, 52.2 per cent. The mortality rate for 31 cases in which total gastrectomy was performed was 30 per cent; in 276 instances of partial gastrectomy, it was 15.2 per cent. The over-all five year survival rate was 6.6 per cent. These studies indicate an increase in operability and resectability rates and a decrease in the mortality rate during the decade.

Pack, McNeer and Booher [315h] report 13 operative deaths among 41 cases in which total gastrectomy was performed, a mortality rate of 31.7 per cent. Five of 37 patients subjected to total gastrectomy had been alive more than three years after operation at the time of writing. Total removal of the stomach was followed with surprisingly little nutritional disturbance.

Lorange [315i] reports on 707 cases recorded between 1919 and 1946. Surgery was performed in 332, and gastric resection was performed in 212. The operative mortality rate was 14.2 per cent; 55 patients survived more than three years and 34, more than five years. Somewhat similar figures are given by other workers.[315j-l]

The surgical treatment of cancer of the cardia is discussed in detail by Pack and McNeer [315m]; the mortality rate in a series of 65 cases was 32 per cent.

Gastroscopic Appearance of Partially Resected Stomach.—Paulson and Gladsden [316] performed gastroscopic examination as early as the ninth postoperative day without untoward results. Shortly after the operation, the alterations were usually localized about the stoma and consisted of edematous areas, with or without erythema. In contrast,

316. Paulson, M., and Gladsden, E. S.: Partial Gastrectomy: The Clinical Gastroscopic and Radiological Considerations, Gastroenterology **10**:970, 1948.

the later changes tended to be more diffuse, with thickening, erythema, friability and, occasionally, edema; the later changes were variable, being reversible even to normal, but they were recurrent. Roentgenologic examination rarely revealed any anatomic or functional change. No consistent relation existed between hypoproteinemia and mucosal edema. No correlation was demonstrated between symptoms and milder anatomic alterations noted on gastroscopic study, although severe changes usually were accompanied with symptoms.

Metabolic Effects After Total Gastrectomy.—The cases of 3 patients who had survived total gastrectomy for three, five and ten years, respectively, were carefully studied by MacDonald and his associates.[317] All patients experienced hunger and had a normal desire for food. Roentgenologic examination revealed a normal esophagus and a wide esophagojejunal opening. Glucose tolerance tests indicated early, pronounced hyperglycemia of short duration. In 1 patient, in whom part of the pancreas had been removed, the output of pancreatic enzymes and the absorption of fat were impaired. Transection of the vagus nerve was complete in each case, but biliary and intestinal functions were not disturbed as a consequence. Pancreatic function was apparently normal in the 2 cases with an intact pancreas. Macrocytic hyperchromic anemia developed in 2 patients two and five years after operation, respectively.

Two patients who underwent partial gastrectomy early in life were followed up for twenty-one and thirty years[318]: Normal physical development and excellent health were the experience of 1 patient; half of that person's stomach, containing a leiomyoma, had been removed when she was 10. In the second case approximately a fourth of the stomach, containing a fibroma, was removed when the patient was 16. She developed normally after operation and remained well for thirty years, except for some difficulty in maintaining body weight.

Irradiation.—In 15 of 32 cases, treatment was by direct irradiation at the time of operation; in 6 of these the disease appeared to be limited to an area that could be irradiated. Among the patients of this group, 1 lived twenty-four months after treatment; 2, fifteen months; 1, seven months; 1, four months, and 1, three months. A maximum dose of 3,000 r for three minutes was directed over a field of 13 sq. cm.[319]

317. MacDonald, R. M.; Ingelfinger, F. J., and Belding, H. W.: Late Effects of Total Gastrectomy in Man, New England J. Med. **237**:887, 1947.

318. McGuff, P., and Morlock, C. G.: Report of Prolonged Follow-Up Study of Two Patients Who Underwent Partial Gastrectomy When Young, Gastroenterology **9**:307, 1947.

319. Fairchild, G. C., and Shorter, A.: Irradiation of Gastric Cancer, Brit. J. Radiol. **20**:511, 1947.

PEPTIC ULCER

Survey of Investigations.—Sandweiss,[320] in an informative article, reports the results of a survey of the current status of investigations on peptic ulcer conducted by the American Gastroenterological Association's committee for the study of peptic ulcer. The survey discloses a distinct need for better coordination, greater and more organized financial support, a larger number of trained investigators and improvement in the means of disseminating the results of research.

Experimental Observations.—Gross and microscopic studies were made of operative defects and of sutured incisions in the gastric wall of normal dogs and of animals receiving daily injections of histamine in yellow wax.[321] Spontaneous ulcers were not observed in approximately 100 normal dogs. Artificial defects in the gastric wall and lines of incision all manifested relatively rapid healing. In dogs with hyperacidity, on the contrary, spontaneous ulcers, artificial defects and sutured incisions all gave evidence of inflammation, necrosis and autodigestion. The severity of the erosive process was roughly proportional to the acidity of the gastric content when the animal was fasting. These two conditions, failure to repair and normal repair, could be induced by the administration or the withdrawal of histamine.

Ulcerations of the stomach and/or the duodenum were produced in each of 5 dogs receiving tenth-normal solution of hydrochloric acid per gastrostomy opening continuously, at the average rate of 71 to 83 cc. per hour, for fifty and one-half to ninety hours.[322] One animal died as a result of perforation of ulcer. Four dogs had only duodenal ulcer; the fifth had both gastric and duodenal ulceration. Gastritis, varying in degree, was present in all the animals. All refused food. Severe acidosis was present in the 2 dogs examined. In a second series of 9 dogs receiving a similar amount of acid per gastrostomy opening, but in which the p_H of the blood was maintained at a normal level by the introduction of 0.16 normal solution of sodium bicarbonate, administered either through an incision for ileostomy or by continuous intravenous infusion at an average rate of 38 to 98 cc. per hour, for periods of from fifty-four and one-half hours to two hundred ninety-two and one-half hours, the development of ulceration was prevented in all but 1. The formation of a duodenal ulcer in this dog was ascribed to an

320. Sandweiss, D. J.: The Present Status of Investigations on Peptic Ulcer: Report of a Survey by the National Committee of American Gastroenterological Association for the Study of Peptic Ulcer, Gastroenterology **9**:335, 1947.

321. Price, P. B.: Repair in the Normal and Hyperacid Stomach, Surg., Gynec. & Obst. **86**:59, 1948.

322. Cummins, G. M.; Grossman, M. I., and Ivy, A. C.: An Experimental Study of the Acid Factor in Ulceration of the Gastrointestinal Tract in Dogs, Gastroenterology **10**:714, 1948.

inadequate supply of base, with consequent lowering of the p_H of the blood. With few exceptions, the normal electrolyte equilibrium was maintained in these animals. Gastritis was present in 5 and duodenitis, in 4; in 4, the gastric and duodenal mucosa appeared normal.

In further experiments, Heidenhain gastric pouches were constructed in three series of dogs,[323] differentiated on the basis of primary closure of the pouch, secondary closure, and primary closure combined with daily aspiration of the pouch. Acute ulcers with perforation developed in the majority of closed pouches. Intraluminal pressure apparently enhanced the ulcer-producing capacity of the gastric content.

Lillehei, Wangensteen and their associates[324] continue their interesting studies on abetting factors in histamine-induced ulcer in dogs. Muscular fatigue depressed the output of acid and volume of gastric juice in dogs with Heidenhain pouches, under basal conditions and after stimulation with histamine. However, the fatigue favored the development of ulceration.[324a] Ulcers were induced with histamine more readily in dogs in which anemia and shock were produced than in normal animals or in dogs with anemia only.[324b] The oldest animals were the most susceptible, whereas pups from 3 to 8 months of age were most resistant.[324c] Postganglionic sympathectomy increased the susceptibility to histamine-induced ulcer.[324d] At the time of writing, the increased susceptibility had continued in 1 instance for four hundred and ninety-nine days after celiac ganglionectomy. Loops of jejunum in 12 dogs were perfused with gastric juice for six and one-half to twelve and one-half hours.[324e] The gastric juice was obtained from dogs with gastric pouches by stimulation with either histamine or pilocarpine hydrochloride mixed with beeswax; the pilocarpine-stimulated gastric juice produced the greater degree of necrosis. It is suggested that the proteolytic activity of gastric juice is due to an increase of both acid and pepsin rather than of acid alone,

323. Stein, I. F., Jr.; Grossman, M. I., and Ivy, A. C.: Experimental Production of Ulcers in Closed Gastric Pouches in Dogs, Surgery **22**:522, 1947.

324. (*a*) Lillehei, C. W., and Wangensteen, O. H.: Effect of Muscular Fatigue on Histamine-Provoked Ulcer with Observation on Gastric Secretion, Proc. Soc. Exper. Biol. & Med. **67**:49, 1948. (*b*) Lillehei, C. W.; Dixon, J. L., and Wangensteen, O. H.: Relation of Anemia and Hemorrhagic Shock to Experimental Ulcer Production, ibid. **68**:125, 1948. (*c*) Lillehei, C. W., and Wangensteen, O. H.: Effect of Age on Histamine-Induced Ulcer in Dogs, ibid. **68**:129, 1948; (*d*) Effect of Celiac Ganglionectomy upon Experimental Peptic Ulcer Formation ibid. **68**:369, 1948. (*e*) Dameron, J. T., and Wangensteen, O. H.: The Effects Produced by Perfusion of the Jejunum with Histamine and Pilocarpine-Stimulated Gastric Juice, Gastroenterology **10**:859, 1948. (*f*) Friesen, S. R.; State, D.; Jasper, D. E.; Finn, M., and Wangensteen, O. H.: Production of Allergic Gastric and Duodenal Edema which Predisposes to the Histimine-Provoked Ulcer in Dogs, Surgery **23**:167, 1948.

and that proteolytic enzymes play a role in perforation of the intestine secondary to obstruction. In studies of the possible role of allergic factors, 12 dogs were sensitized locally with immune hare serum of high antibody titer and then were given antigens intravenously, as well as the usual histamine in beeswax. Edema with ulcer and/or erosion were noted at the site of sensitization.[324f]

The oral administration of enterogastrone is reported to have exerted some beneficial therapeutic effect on experimental Mann-Williamson ulcers in dogs.[325] In the opinion of the reviewers, the differences between the control animals and those treated were not striking. The results, furthermore, are in contrast to the observations of other investigators, as noted by the authors.

The postoperatitve period of survival for dogs subjected to both the Mann-Williamson operation and transthoracic vagotomy was much shorter than that for control animals.[326] Ulcer developed in 6 of 8 dogs surviving one month after both operations. Gastric dilatation was present in 75 per cent of the vagotomized dogs and jejunitis, of varying severity, in 60 per cent. Since bilateral vagotomy failed to prevent the development of Mann-Williamson ulcers and is beneficial in man, Oliver[327] concludes that the etiology of ulcer in man differs from that in the dog. Vagotomy likewise had no protective effect against the development of cinchophen-induced ulcers.[328]

Histamine-induced ulcers in guinea pigs were not prevented with diphenhydramine hydrochloride (benadryl hydrochloride®) administered daily, either as an aqueous solution orally or subcutaneously or in yellow wax subcutaneously.[329] Vagotomy also failed to prevent the induction of ulcers with histamine in guinea pigs. Pyloric ligation–induction of ulcers in the rat was prevented by vagotomy, and life was prolonged in survival studies. Average gastric acidity and gastric volume were less in vagotomized rats; however, these were thought to be not the only factors in prevention of ulcer, since in some instances control rats

325. Saltzstein, H. C.; Sandweiss, D. J.; Hammer, J. M.; Hill, E. J., and Vandenberg, H. J., Jr.: Effect of Enterogastrone on Mann-Williamson Ulcers in Dogs, Arch. Surg. **55**:125 (Aug.) 1947.

326. Saltzstein, H. C.; Sandweiss, D. J.; Hammer, J. M.; Hill, E. J., and Vandenberg, H. J., Jr.: Effect of Vagotomy on Mann-Williamson Ulcers in Dogs, Arch. Surg. **55**:130 (Aug.) 1947.

327. Oliver, J. V.: Effect of Vagotomy on Development of the Mann-Williamson Ulcer in the Dog, Arch. Surg. **55**:180 (Aug.) 1947.

328. Hilsabeck, J. R., and Hill, F. C.: Role of the Vagus Nerve in Experimental Cinchophen Ulcer, Proc. Soc. Exper. Biol. & Med. **66**:155, 1947.

329. Harkins, H. N.; Hooker, D. C.; Alford, T. C., Jr.; Callander, J.; Elliott, S. R., II; Kearns, W., Jr.; Mitchener, J., and Cooley, D. A.: Symposium on Vagotomy for Peptic Ulcer: I. Experimental Observations, Bull. Johns Hopkins Hosp. **81**:79, 1947.

with ulcer had smaller gastric volumes and lower acidity than some vagotomized rats without ulcers. Ulcer developed in 85 per cent of 13 dogs subjected to the Mann-Williamson operation. Among 9 vagotomized dogs which had undergone the Mann-Williamson operation, ulcer developed in only 1 during the period of observation. Vagotomy was not performed until an average of fifty-one days had passed after the Mann-Williamson operation.

The importance of the alkaline secretions in the proximal small intestine in neutralization of gastric acidity and prevention of peptic ulcers is discussed by Hanrahan [330] on the basis of a variety of experiments. Segments of jejunum or of the upper portion of the ileum, 10 cm. in length, were opened and implanted in a defect on the greater curvature of the gastric wall, the mesentery being retained. No ulcerations were noted; superficial erosions occurred in 2 animals in which small pouches resulted, containing foreign bodies. Gastric flaps were reimplanted in the gastric wall. No erosion of the mucosa occurred until the pedicle was so narrowed as to cause almost complete loss of the blood supply. The Chlumsky operation (pylorectomy with drainage of duodenal contents into the upper portion of the stomach, and gastrojejunostomy) was performed on 3 dogs; all survived two months and showed chronic marginal ulcers. It was concluded that loss of the neutralizing effect of intestinal content alone did not explain the development of ulcer after the Mann-Williamson operation, since, in the experiments described, direct emptying of the duodenal content into the stomach had no preventive effect.

The parenteral administration of diethylstilbestrol dipropionate in doses of 0.25 to 5.0 mg. daily for periods of twelve to twenty-six days to a group of 38 dogs (23 males and 15 females) is reported to have prevented experimental production of ulcer with cinchophen in 100 per cent of the males and in 22 per cent of the females.[331] Hyperplasia of the gastric mucosa was noted, particularly in the male animals. Confirmation and extension of this interesting observation appear desirable.

Risley, Raymond and Barnes [332] conclude that the "Shay rat" is of value in the assaying of the antisecretory activity of parenterally administered extracts of urine and intestines. None of the preparations was active when given orally. The parenterally administered extracts are thought to have inhibited ulceration by decreasing the volume of secretion and the concentration of acid; there was no specific effect on

330. Hanrahan, E. M.: The Experimental Investigation of Peptic Ulcer, Bull. Johns Hopkins Hosp. **81**:131, 1947.

331. Nasio, J.: Action of Parenteral Stilbestrol in the Prevention of Experimental Cinchophen Peptic Ulcer, Rev. Gastroenterol. **14**:467, 1947.

332. Risley, E. A.; Raymond, W. B., and Barnes, R. H.: The Use of the Shay Rat in Studying Anti-Ulcer Substances, Am. J. Physiol. **150**: 754, 1947.

production of pepsin. No evidence was obtained of ulcer-combating activity other than that of inhibition of secretion. The reviewers regard this experimental assaying as interesting but wish to reemphasize the fact that data so obtained are not necessarily applicable to treatment in man. Extensive ulceration in the rumen of the rat after ligation of the pylorus was inhibited and prevented by the oral, intraperitoneal, subcutaneous and intravenous administration of salicylic acid and of aectylsalicylic acid (aspirin); salicylic acid reduced gastric secretion[333]; it may be noted that this substance is a protoplasmic poison. Tetraethylammonium chloride apparently exerted a preventive effect against ulcers after pyloric ligation in the rat.[334]

Betz,[335] in a detailed study of the effects of irradiation on the stomach of rabbits, observed no toxic effects after irradiation of the stomach alone. Deaths encountered in previous experiments were attributed to irradiation of the intestine. A total of 1,500 r applied to the stomach resulted in rapidly healing superficial ulcerations when the portal measured 10 by 15 cm.; the same dose did not cause ulceration when the field of exposure was 6 by 8 cm. Ulcers were produced with doses larger than 2,000 r. Necrosis and ulceration were preceded by edema of the submucosa, with exudation of fibrin and with fibrinoid degeneration of the collagenous fibers. Compression of the blood vessels by edema is thought to lead to partial necrosis of the gastric mucosa.

Fourteen patients with malignant tumors of the testes received large doses of radiation to the epigastrium for prophylaxis or because of the presence of metastases[336]; apparently all had been free of gastrointestinal symptoms and disease. From 2,424 to 6,456 r were directed principally to the antrum of the stomach. The free acidity varied greatly; no depression of gastric acidity was observed two months or more after irradiation. Gastric ulcer developed in 9 patients, as noted at roentgenologic or gastroscopic examination. Four of these came to operation from ninety-five to two hundred and twenty-three days after treatment; in 3 the ulcer had perforated. The author concludes, in view of these observations, that irradiation has no place in the treatment of

333. Pauls, F.; Wick, A. N., and Mackay, E. M.: Inhibition of Gastric Ulceration in the Rat by O-Hydroxybenzoic (Salicylic) Acid, Science **107**:19, 1948.

334. Little, J. M.; Ogle, B. C.; Teagley, J. D., and Cayer, D.: Effect of Tetraethylammonium Chloride in Experimental Gastric Ulceration in the Rat, Science **106**:448, 1947.

335. Betz, H.: Contribution a l'étude de l'ulcère gastrique: III. Sur la production d'ulcères gastriques par irradiation de l'estomac seul chez le lapin; Essai d'application à la pathogénie de l'ulcère chronique chez l'homme, Rev. belge path. et méd. expér. **28**:143, 1947.

336. Brick, I. B.: The Effect of Large Dosages of Irradiation on Gastric Acidity, New England J. Med. **237**:48, 1947. Bowers, R. J., and Brick, I. B.: Surgery in Radiation Injury of the Stomach, Surgery **22**:20, 1947.

benign gastric ulcer. It should be noted that in the radiation therapy now under investigation by the reviewers as a method of reducing gastric secretion in patients with peptic ulcer, the quantity of radiation is considerably smaller than that used in the reported study; the radiation is administered in divided doses, and it is applied to the upper, acid-secreting portion of the stomach over fluoroscopically outlined portals. In a large series of cases, postradiation ulceration was noted in only 2. Anacidity was invariably accompanied with healing of the ulcer. However, the effect of roentgen irradiation on gastric acidity was variable, unpredictable and usually temporary.

Hamilton,[338] in a similar series of 256 patients with radiosensitive, malignant testicular tumors treated by orchidectomy and massive high voltage roentgen irradiation of the retroperitoneal lymph nodes, found that epigastric distress developed in approximately one-half the patients when the radiation near the stomach, which was normal, exceeded 5,000 r. In 35, a large, single gastric ulcer was demonstrated by fluoroscopy; 6 required operation. All the patients in whom ulcer developed had had a dose of radiation exceeding 5,000 r. However, in some patients receiving doses of radiation greatly in excess of this quantity no ill effects were observed.

Baronofsky [339] found that ligation of three of the large arteries of the stomach and of additional branches from the gastroepiploic arteries failed to protect against histamine-provoked ulcer.

LeVeen,[340] on the other hand, states that ligation of the major gastric vessels can reduce the quantity of hydrochloric acid secreted sufficiently to prevent histamine ulcer. Extensive ligation, however, produces ulceration.

Chaton [341] states that he considers ligation of the coronary arteries to the stomach of value in the treatment of peptic ulcer; healing is attributed to a reduction in secretion. Dodd [342] presents contrasting observations. Ligation of gastric vessels and gastroenterostomy were performed in the case of a man of 44 with duodenal ulcer. A jejunal

337. Footnote deleted.

338. Hamilton, F. E.: Gastric Ulcer Following Radiation, Arch. Surg. **55**:394 (Oct.) 1947.

339. Baronofsky, I. D.: An Experimental Evaluation of Ligature of Stomach Vessels for Peptic Ulcer, Gastroenterology **10**:301, 1948.

340. LeVeen, H. H.: The Effect of Surgical Interruption of the Gastric Blood Flow upon Gastric Secretion and the Prevention of Experimental Peptic Ulcers, Surg., Gynec. & Obst. **86**:164, 1948.

341. Chaton, M.: La question des ligatures arterielles dans le traitement de la maladie ulcereuse gastrique, France méd. **12**:10, 1947.

342. Dodd, H.: Anastomotic Ulcer Twelve Months After Somervell Operation, Brit. M. J. **2**:170, 1947.

ulcer developed approximately seven months later. One year after operation, a partial gastrectomy was carried out owing to the presence of a large gastric ulcer.

Sturm [343] postulates that gastric angiospasm producing local ischemia is a factor in the pathogenesis of peptic ulceration.

A study was made of the vascularity of the stomach in 200 cases in which resection was done for chronic peptic ulcer.[344] The resection was carried out under spinal anesthesia; one or more main arteries were injected with iodized oil under roentgenologic control, and films were taken at intervals. The cut edges of the specimens were carefully ligated to avoid loss of the injected oil. Control observations were not obtained, since normal stomachs obviously could not be examined by the same technic. The arterial anastomoses were found to be so rich that it was difficult to see how an ulcer could have resulted from local arterial disease. The connective tissue about the ulcer, with its concomitant obliterating arteritis, interrupted the normal anastomosing plexuses, but, to compensate for this, all the vessels of all the gastric layers contributed a dense periulcerous network. The blood supply of the antrum is normally less than that of the body of the stomach, but it was increased in cases of ulcer. The author concludes that peptic ulcer does not develop on the basis of alterations in the vascularity of the stomach or the duodenum. However, there occur secondarily an increase in reticulin and diminished vascularity in the region of callous ulcers of the stomach; the decreased vascularity probably contributes to the chronicity of the lesion.[345] Betz,[346] on the basis of detailed anatomic studies, states that neither embolism nor arteriosclerosis plays a pathogenic role in the development of peptic ulcer, that arterial occlusions are consequences of local circulatory disturbances and not of arterial inflammation, and that allergic origin is possible. Circulatory disturbances are presumed only to localize the allergic reaction.

Role of Acid in Gastric Secretion.—The various theories concerning the pathogenesis of peptic ulcer are reviewed by a number of

343. Sturm, A.: Biphasic Disturbance in Innervation of Wall of Stomach in Presence of Ulcer: Analysis of Neurosympathetic Condition of Stomach with Ulcer, Deutsche med. Wchnschr. **73**:158, 1948.

344. DeBusscher, G.: The Vascularization of the Ulcerated Stomach, Gastroenterologia **22**:154, 1947.

345. DeBusscher, G.: Etude comparative du degré de gastrite de l'intensité de la formation de reticuline et de la vascularisation de l'estomac ulcereux, Acta gastroenterol. belg. **10**:375, 1947.

346. Betz, H.: Contribution a l'étude de l'ulcère gastrique: II. Etude anatomopathologique de l'ulcère chronique chez l'homme, Rev. belge path. et méd. expér. **18**:3, 1947.

writers,[347] with the conclusion that the lesion results from acid digestion of an area of diminished resistance. Deelman [347d] states that the ulcer begins as a fissure in the mucous membrane and penetrates down into the muscle. Atrophy of Brunner's glands, which may be brought about by excessive muscular contraction, with subsequent increased vulnerability of the surface epithelium, is regarded as an important factor. The preponderance of duodenal ulcer as compared to gastric ulcer is ascribed to two factors, (*a*) abundant innervation of the upper portion of the duodenum and (*b*) special protoplasmic organization of the duodenal cells, rendering them particularly vulnerable to acid gastric juice.[347e]

Voegtlin,[348] in a study of the nocturnal gastric secretion of 13 presumably normal persons hospitalized because of seasickness, and of 53 patients with uncomplicated duodenal ulcer, concludes that the mean nocturnal free acidity did not vary significantly in the two groups. The values for approximately 20 per cent of the patients with ulcer were higher than normal, whereas an equal number were lower. Neither the injection of 0.01 grain of atropine at 9:00 p. m. nor the administration of milk and alkali at night at two hour intervals significantly decreased nocturnal acidity. Cottonseed oil or oleic acid in the stomach apparently inhibited gastric acidity to a slight degree approximately four to six hours later. In contrast to well established results of previous observations, insoluble antacids are reported to have caused slight and inconstant lowering of gastric acidity; gastric lavage with solution of sodium bicarbonate at 9:00 p. m. did not tend to decrease the nocturnal acidity. Nocturnal gastric acidity in cases of uncomplicated duodenal ulcer did not show a tendency to decrease as healing occurred.

Levin, Kirsner, Palmer and Butler compared the values for volume and hydrochloric acid content of the twelve hour nocturnal gastric secretion for patients with duodenal ulcer, gastric ulcer and gastric carcinoma with the values for normal subjects.[349a] The volume and output of hydrochloric acid were usually highest for patients with duo-

347. (*a*) Doyle, L.: Peptic Ulcer, M. J. Australia **34**:34, 1947. (*b*) Dauwe, F.: Dehongermaageweer, Bldg. tijdschr. Geneesk. **3**:241, 1947. (*c*) Daron, P. B.: The Etiology of Peptic Ulcer, New Orleans M. & S. J. **100**:163, 1948. (*d*) Deelman, H. T.: Genesis of Duodenal Ulcers, Nederl. tijdschr. v. geneesk. **91**:1769, 1947. (*e*) Schiassi, B.: Reasons for the Ratio of Incidence (Approximately 5:1) of Duodenal to Gastric Ulcer, Policlinico (sez. prat.) **54**:42, 1947.

348. Voegtlin, W. L.: Gastric Acidity in Normal Individuals and Those with Uncomplicated Duodenal Ulcer: An Attempt to Influence the Nocturnal Secretion, Gastroenterology **9**:125, 1947.

349. Levin, E.; Kirsner, J. B.; Palmer, W. L., and Butler, C.: (*a*) The Fasting Nocturnal Gastric Secretion in Normal Individuals and in Patients with Duodenal Ulcer, Gastric Ulcer and Gastric Carcinoma, Arch. Surg. **56**:345 (March) 1948; (*b*) The Variability and Periodicity of the Nocturnal Gastric Secretion in Normal Individuals, Gastroenterology **10**:939, 1948; (*c*) A Comparison of the Nocturnal Gastric Secretion in Patients with Duodenal Ulcer and in Normal Individuals, ibid. **10**:952, 1948.

denal ulcer. For a small series of patients with gastric ulcer the average volume of gastric juice was approximately the same as that for normal subjects, but the average acid content was lower. The nocturnal gastric secretion was lower for patients with gastric carcinoma than for normal subjects or for persons with gastric ulcer. The secretion of gastric juice in normal persons is apparently continuous; however, the secretion of hydrochloric acid is not continuous in all persons.[349b] The volume of secretion and output of acid are usually higher during the first half of the night than during the last half. A wide individual variation and a considerable spontaneous variation of the gastric secretion for the same person may be observed from hour to hour and also from night to night.

In further studies,[349c] it is noted that the secretion of acid gastric juice in patients with duodenal ulcer was continuous. Although individual variations existed, a high output of acid on one night, in the vast majority of instances, was duplicated on successive nights. A similar rule also held true for patients with a low secretory rate. The rate of gastric secretion was not constant but varied spontaneously from hour to hour in the same person.

Beretta,[350] in a report from Italy, states that the output of acid in the gastric secretion is increased in fasting patients with either duodenal ulcer or gastric ulcer. Hypersecretion depends not so much on the site of the ulcer as on the "individual neurovegetative state." Hypersecretion is much more frequent and the acidity curves are higher and more prolonged for patients with duodenal ulcer than for those with gastric ulcer. As noted by others, the value for gastric acidity varied considerably for the same person on successive days.

A comparative study of the effect of five antacids on the gastric secretion was made on 2 dogs with Cope gastric pouches.[351] The antacids were sodium bicarbonate, sodium citrate, aluminum hydroxide gel, calcium carbonate and magnesium oxide. Consistent increases in the volume of secretion and of hydrochloric acid were observed when sodium bicarbonate and calcium carbonate were given. Magnesium oxide caused increased secretion in 1 animal, but not in the other. None of the antacids produced a significant decrease in secretion during the nine hours following the test meal. The observation concerning calcium carbonate is in contrast to the effectiveness of that antacid in treatment of patients with peptic ulcer, as noted by

350. Beretta, A.: Gastric Secretion in Relation to the Site of the Gastric and Duodenal Ulcer, Gior. ital. chir. **3**:413, 1947.

351. Clark, B. B., and Adams, W. L.: The Effect of Gastric Antacids on Gastric Secretion as Observed in the Cope Pouch Dog: Sodium Bicarbonate, Aluminum Hydroxide Gel, Calcium Carbonate, Magnesium Oxide and Sodium Citrate, Gastroenterology **9**:284, 1947.

other investigators. Clark[352] found that the inhibitory effect of amprotropine phosphate (syntropan®), meperidine hydrochloride (demerol hydrochloride®) or trasentin® (hydrochloride of diphenylacetyldiethylaminoethanol) on the gastric secretion of the dog was relatively weak in comparison with the effect of atropine. Atropine, on the basis of weight, exceeds the activity of syntropan® and of demerol hydrochloride® by 1,000 to 3,000 times and that of trasentin® by over 3,000 times.

Kirsner, Levin and Palmer[353] studied the effects of an enterogastrone concentrate on noctural and twenty-four hour gastric secretion in 14 cases of peptic ulcer. The twenty-four hour gastric secretion may decrease after the intramuscular injection, in divided amounts, of 1,000 to 3,000 mg. of the concentrate. The inhibition is variable in degree and not consistently related to the dosage of enterogastrone. A reduction in secretion may occur rather promptly after the injection of large quantities of enterogastrone but usually does not persist for longer than twenty-four hours. The inhibition consists chiefly of a pronounced reduction in the concentration of acid. The volume of gastric secretion may be lowered slightly or moderately or may remain unchanged. The inhibitory effect may be overcome by the psychologic stimulus of anger. In some cases, the secretion of acid increased during the administration of enterogastrone and also twenty-four and forty-eight hours later. A single injection of 5,000 mg. of enterogastrone did not demonstrably lower the twenty-four hour gastric secretion in a case of duodenal ulcer. Sixteen experiments were performed, in 15 cases of peptic ulcer, on the effect of moderately large quantities of an enterogastrone concentrate on the response of the gastric secretion to histamine and to insulin.[354] The intramuscular injection of 400 to 2,000 mg. of an enterogastrone concentrate did not significantly affect the secretory response of the human stomach to the single average dose of histamine or to the repeated injection of small quantities of histamine. The administration of 1,000 mg. of enterogastrone did not alter insulin-stimulated gastric secretion. The administration of 2,000 to 3,000 mg. of the concentrate apparently modified the response of the gastric secretion to insulin in several cases, but further studies are considered necessary.

352. Clark, B. B.: A Comparison of the Effect on Gastric Secretion of Syntropan, Demerol, and Trasentine with Atropine, Gastroenterology **9**:454, 1947.

353. Kirsner, J. B.; Levin, E., and Palmer, W. L.: Studies on Nocturnal Twenty-Four-Hour Gastric Secretion During the Injection of an Enterogastrone Concentrate in Man, Gastroenterology **10**: 246, 1948.

354. Levin, E.; Kirsner, J. B., and Palmer, W. L.: Preliminary Observation on Histamine and Insulin Stimulated Gastric Secretion During the Injection of an Enterogastrone Concentrate in Man, Gastroenterology **10**:274, 1948.

The output of hydrochloric acid in the twelve hour nocturnal gastric secretion in 10 cases of peptic ulcer after the intramuscular injection of 20 cc. of aolan® (sterile solution of lactalbumin in colloidal form) was unchanged in 3 cases, decreased slightly in 1 and increased in 6.[355] The results suggest that the temporary reduction in gastric secretion occasionally observed during the administration of enterogastrone is not attributable to a nonspecific action of the proteins present in the concentrate.

The effect of varying doses of an amino acid preparation on gastric acidity (as determined with an Ewald test meal) was observed for 16 persons: Five were apparently normal, 3 had functional digestive disorders and 8 had peptic ulcer.[356] Repeated administration of small amounts of amino acids was comparatively ineffective in reducing gastric acidity and caused a high rebound acidity. Single large doses (50 Gm.) reduced gastric acidity to zero for approximately one and one-half hours but also produced a high secondary response.

Breitwieser[357] noted a temporary decrease of peptic activity in 2 persons without gastrointestinal disease and in 2 patients with peptic ulcer, all of whom received 0.6 Gm. of sodium alkyl sulfate. These observations, confirming the previous observations of Kitsner and Wolff, indicate that the detergent is not of value in the treatment of peptic ulcer.

The effect of tetraethylammonium chloride on gastric secretion and motility was studied in 10 cases.[358] The concentration of free hydrochloric acid was reduced by an average of 62 per cent for thirty to sixty minutes when tetraethylammonium chloride was given intravenously in 5 cases, and by an average of 44 per cent for two to three hours when tetraethylammonium chloride was given intramuscularly in 5 cases. Chlorides were reduced by approximately 25 per cent. A complete cessation of gastric motility persisted for approximately the same length of time as the reduction in gastric acidity. The pain of ulcer, present in 2 cases at the time of injection of tetraethylammonium chloride, disappeared simultaneously with the cessation of gastric motility. The authors point out that the possible therapeutic usefulness of the drug is limited because of its relatively short duration of action and because of untoward side effects.

355. Kirsner, J. B.; Levin, E., and Palmer, W. L.: Effect of Non-Specific Protein (Aolan) upon Twelve-Hour Nocturnal Gastric Secretion in Man, Proc. Soc. Exper. Biol. & Med. **68**:90, 1948.

356. Feller, J., and Tidmarsh, C. J.: The Effect of Amino Acids on Gastric Acidity, Canad. M. A. J. **57**:23, 1947.

357. Breitwieser, E. R.: The Effect in Vivo of Sodium Alkyl Sulphate on Peptic Activity, Gastroenterology **9**:81, 1947.

358. Brown, H. S.; Posey, L., Jr., and Gambill, E. E.: Studies on the Effect of Tetraethylammonium Chloride on Gastric Motor and Secretory Function in Patients with Duodenal Ulcer, Gastroenterology **10**:837, 1948.

Majone[359] observed a considerable difference in the lytic action of the saliva on gastric mucin of patients with gastric ulcer as compared with that of normal persons. The output of mucin and the response of gastric secretion to stimulus with alcohol did not differ between a group of normal subjects and a group of patients with duodenal ulcer.[360]

Disturbances in Blood Chemistry and Metabolism.—Ten of 60 patients with gastric or duodenal ulcer were found to have increased histamine in the blood.[361] No apparent correlation was noted between the secretion of hydrochloric acid and the histamine in the blood. No difference was observed between values for patients with gastric ulcer and those for patients with duodenal ulcer. Histamine levels in the blood apparently increased after dietary treatment and administration of aluminum hydroxide.

Surkes[362] determined the histamine levels in the whole blood in 40 cases of peptic ulcer; they were normal in 28, slightly increased in 8 and greatly increased in 4. The histamine values were normal in 15 of 19 cases in which the niche had disappeared; they were slightly increased in the remaining 4. The blood histamine was measured before and immediately after gastrectomy in 4 cases; the values tended to decrease after operation.

Alpern[363] found demonstrable amounts of acetylcholine in the blood in approximately 85 per cent of 190 cases of active peptic ulcer. Fifty patients with chronic gastritis, cholecystitis or gastric cancer served as controls; for none of these was acetylcholine demonstrated. According to the author, the amount of acetylcholine varied directly with the severity of symptoms, and the titer fell gradually to zero when the ulcer was healed. No protocols are given in support of these assertions. Alpern states the belief that prolonged stimulation of the vagus nerve leads to the excessive production of acetylcholine, which in turn causes spasm of the gastric arterioles and of the muscularis mucosae. In the presence of concomitant hypersecretion, this

359. Majone, P.: Il potere litico della saliva degli ulcerosi sulla mucina gastrica in rapporto alla patogenesi dell'ulcera gastrica, Riforma med. **61**:297, 1948.

360. Tulin, M.; Gutmann, J., and Almy, T. P.: The Secretion of Gastric Mucin Following Alcohol Meal: Studies on Normal Subjects and on Patients with Peptic Ulcer, Gastroenterology **9**:191, 1947.

361. Lips, A. C. M.; Verschure, J. C. M., and Strengers, T.: The Histamine Level of the Blood in Patients with Gastric or Duodenal Ulcer Before and After Treatment with Aluminum Hydroxide, Acta med. Scandinav. **129**:274, 1947.

362. Surkes, A. W.: Histamine Contents of Blood in Patients with Ulcers, Praxis **37**:264, 1948.

363. Alpern, D. E.: Blood Acetylcholine in Gastrointestinal Ulcer, Presse méd. **55**:555, 1947.

ischemia of the mucosa is presumed to lead to "autodigestion" and ulceration. The concept is of interest in relation to the physiologic basis for vagotomy, but the data require confirmation by others.

No differences in the levels of serum potassium, calcium or magnesium or of blood lipids were observed between normal persons and patients with peptic ulcer.[364] Hepatic function in 68 men with peptic ulcer, as estimated by the oral hippuric acid test, is reported as lower in many patients than in those observed in a control group; in most instances, the amount of excretion increased when the patient's general condition improved[365]; no other tests of hepatic function are recorded, and no details of the clinical condition of the patients are given. In 25 cases of gastric or duodenal ulcer,[366] histologic examination of biopsy specimens of the liver disclosed leukocytic infiltration of the portal spaces, vascular degeneration of cells and infiltration by polymorphonuclear leukocytes between the cells of the hepatic lobes. The reviewers believe that the examination of normal persons of comparable ages and of patients with other diseases is desirable in order properly to evaluate the observations.

Goldschmied[367] reports comparatively low figures for blood sugar in cases of peptic ulcer. Peskin[368] states that he considers some of the symptoms produced by "mild hypoglycemia" to be similar to ulcer distress.

Nutritional Factors.—Dauwe[369] states that malnutrition plays an important role in the development of ulcer. In cases of ulcer and anemia in which a diet of raw meat pretreated with gastric juice from healthy persons was given[370], the lesions healed with unexpected rapidity. The author postulates, on this rather tenuous evidence, the existence of a protective factor in normal gastric juice and of an activating principle in fresh meat.

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364. Soisalo, P., and Vavtizinen, I.: Studies on Blood Potassium, Calcium, and Lipids in Peptic Ulcer, Ann. med. int. Fenniae **36**:647, 1947.

365. Pollak, H.: Hepatic Dysfunction in Peptic Ulcer, Lancet **2**:131, 1947.

366. Cora-Jannopoulos, M. J.: Les lesions hépatiques dans les ulcères de l'estomac et du duodenum, read before the Société de médecine de Paris, Jan. 23, 1948.

367. Goldschmied, A.: Contribution a l'étude de la glycemie au cours de la maladie ulcereuse de l'estomac et du duodenum et des affections inflammatoires, Gastroenterologia **73**:209, 1948.

368. Peskin, A. R.: Increased Sugar Tolerance as a Factor in the Production of a Symptom Complex Simulating Peptic Ulcer, Neuro-Circulatory Asthenia, and Psychoneurosis, Am. J. Digest. Dis. **15**:92, 1948.

369. Dauwe, F.: Gastric Ulcer by Malnutrition, Belg. tijdschr. u. geneesk. **3**: 241, 1947.

370. Boller, R.: The Origin and Casual Treatment of Gastric Ulcer, Wien. med. Wchnschr. **97**:93 and 115, 1947.

Cayer and Cody[371] measured vitamin levels in the blood and urine and state the conclusion that patients with peptic ulcer are not likely to show deficiency of vitamin A, niacin or riboflavin. There is little to suggest, say the authors, that an underlying, preceding deficiency of vitamin A, ascorbic acid, niacin or riboflavin is an etiologic factor in the development of peptic ulcer; the need for the routine administration of these substances in the management of peptic ulcer is doubtful. The observations coincide with the experience of the reviewers.

Wartime Incidence of Ulcer.—Feldman[372] notes a slight increase in the incidence of gastric ulcer during the war period, a 4 per cent rise in duodenal ulcer during and immediately after the war, and an increase in the severity of symptoms, in the number of acute ulcers and in the incidence of hematemesis in female patients. Similar rises are reported from Finland[373] and from the Netherlands.[374]

The end results of treatment in 292 cases of peptic ulcer, with special reference to the effects of wartime conditions in London are evaluated by Douglas.[375] Of 211 patients traced, 40 were dead and 171, alive; the average follow-up period was 6.09 years. Partial gastrectomy is considered to have given the best end result in gastric ulcer and either gastrectomy or gastroenterostomy to have been preferable to medical treatment in duodenal ulcer, with or without stenosis. The author concludes that wartime conditions in London had little effect on the ultimate results of treatment, except that the recurrence rate after conservative measures seems to have been somewhat higher. A mortality rate of 11.5 per cent was noted after gastrectomy for gastric ulcer.

Pain Due to Ulcer.—Bloomfield[376] expresses the belief that two main types of pain occur in cases of peptic ulcer. One type is caused by penetration of the lesion through the mucosal and muscular layers of the stomach and duodenum; steady in type, it is probably due to

371. Cayer, D., and Cody, S.: The Nutritional State of Patients with Peptic Ulcer as Measured by Vitamin Levels in the Blood and Urine, Gastroenterology **9**:54, 1947.

372. Feldman, M.: A Statistical Study of One Hundred and Twelve Cases of Benign Gastric Ulceration, Am. J. M. Sc. **215**:13, 1948; Statistical Study of Life Cycle of 1,154 Cases of Duodenal Ulcer, J. A. M. A. **136**:736 (March 13) 1948.

373. Saksela, N.: War-Time Incidence of Peptic Ulcer: Its Predisposing Causes and Some Simultaneous Symptoms of Other Diseases, Ann. med. int. Fenniae **36**:167, 1947.

374. Boerema, I.: Les affections gastrointestinales in Hollande durand l'occupation, Rev. méd. Liege **2**:253, 1947.

375. Douglas, D. M.: Chronic Ulcer of the Stomach and Duodenum, Brit. J. Surg. **35**:76, 1947.

376. Bloomfield, A. L.: Peptic Ulcer, M. Clin. North America **32**:313, 1948.

peritoneal irritation. The other and commoner variety of pain, so-called ulcer pain, consists of epigastric discomfort, fulness or burning, with occasional regurgitation of sour material or belching of gas, occurs at regular intervals after eating and is relieved by ingestion of food or alkalis. According to Rivers,[377] the pain of peptic ulcer perforating to the pancreas is as a rule localized to an area about the umbilicus and usually extends through to the back. Nervous manifestations and postural methods for obtaining relief often prompt psychiatric consultation.

Diagnosis.—Clinical Diagnosis: Friedman[378] studied the conditions of 138 soldiers with upper abdominal distress related to the ingestion of food; 46 had peptic ulcer and 92, a condition diagnosed as "functional dyspepsia." The symptoms of the patients with ulcer were much like those encountered in civilians of the same age group. For the differential diagnosis of peptic ulcer and of functional dyspepsia, the Palmer provocative acid test is considered indispensable. No evidence is adduced that the strain of military service, including combat, was associated with an increase in the frequency of peptic ulcer.

Roentgenologic Diagnosis: Detection of a crater is the most reliable roentgenologic evidence that a duodenal ulcer is active.[379] Periodic observation of a crater in a duodenal ulcer is a valuable aid in judging the effect of medical management. The roentgenologic aspects of peptic ulcer are discussed further by Singleton[380] and by Gueret.[381] In a well illustrated article, Ball and others[382] state that ulcer located distal to the bulb of the duodenum manifests a smooth, rounded indentation of the wall at the level of the crater, with an eccentric narrowing; the ulcer crater is not always seen.

Gastroscopic Diagnosis: Gastroscopic examination in 50 cases of duodenal ulcer disclosed normal mucosa in 12 and hyperplastic mucosa in 38; concomitant superficial changes were observed in 3.[383]

377. Rivers, A. B.: The Syndrome of Peptic Ulcer Perforating to the Pancreas: Preliminary Report, Proc. Staff Meet., Mayo Clin. **22**:290, 1947.

378. Friedman, M. H.: Peptic Ulcer and Functional Dyspepsia in the Armed Forces, Gastroenterology **10**:586, 1948.

379. Templeton, F. E.: The Crater in Uncomplicated Duodenal Ulcer, Am. J. Roentgenol. **59**:87, 1948.

380. Singleton, A. C.: Radiological Aspects of Peptic Ulcer, Canad. M. A. J. **58**:338, 1948.

381. Gueret, M.: Un moyen simple de realiser la compression debut avec prise de cliches en serie, Arch. d. mal de l'app. digestif **37**:391, 1948.

382. Ball, R. P.; Segal, A. L., and Golden, R.: Post Bulbar Ulcer of the Duodenum, Am. J. Roentgenol. **59**:90, 1948.

383. Freeman, H.: Gastroscopic Studies of the Gastric Mucosa in Duodenal Ulcer, Arch. argent. de enferm. d. ap. digest. y de la nutrición **22**:172, 1947.

Peptic Ulcer in Elderly Persons.—In a series of 1,800 successive cases of peptic ulcer no symptoms referable to the ulcer were noted prior to the patient's reaching the age of 60 in 81 cases (4.5 per cent).[384] Complications of ulcer on admission of the patient to the hospital were noted in 58 per cent; hemorrhage was the chief complaint in 38 per cent; the mortality in this group, in which all treatment was medical, was 10.7 per cent. Perforation constituted the initial evidence of ulcer in 13.8 per cent; the mortality with this complication was high.

One-half of a series of patients from the sixth to the eighth decade of life, with symptoms sufficiently severe to require hospitalization, gave histories of less than two years' duration of the symptoms.[385] Hemorrhage is commoner than perforation. Spang[386] states the belief that arteriosclerosis may play a role in the pathogenesis of peptic ulcer among persons over 50, but no evidence is presented.

Interesting Gastric Ulcers.—In 5 cases in which the patients had vague symptoms and in which the results of roentgenologic examination were indefinite, gastroscopic examination revealed a single large superficial ulcer in the region of the angulus.[387] The ulceration was flat, appearing to involve only the mucosa; the edges were well defined. The ulcer disappeared rapidly on treatment. Ulcers of the posterior wall of the stomach, as described by Bernard and Denecher,[388] tend to cause pain localized in the left hypochondrium; the pain may radiate to the precordium and simulate that of angina pectoris. A large ulcer was found on the posterior wall of the stomach of a boy of 16.[389] An enormous benign ulcer, so large that it simulated a diverticulum, healed after medical treatment.[390] A gastric ulcer was demonstrated roentgenologically in the case of an infant of 6 months.[391] Two patients with benign gastric

384. Rafsky, H. A.; Weingarten, M., and Krieger, C. I.: Onset of Peptic Ulcer in the Aged, J. A. M. A. **136**:739 (March 13) 1948.

385. Lasher, E. P.: The Course of Peptic Ulceration in Elderly Persons, Surgery **23**:501, 1948.

386. Spang, K.: Gastroduodenal Ulcers in the Elderly: Clinical Aspects and Pathogenesis, Deutsche med. Wchnschr. **72**:605, 1947.

387. Moutier, M., and Cornet, A.: La grande ulceration plate de l'estomac, Arch. d. mal. de l'app. digestif **36**:255, 1947.

388. Bernard, A., and Denecher, J.: Reflexions sur 70 cas d'ulcères de la face posterieure de l'estomac, Arch. d. mal. de l'app. digestif **36**:457, 1947.

389. Courty, L., and Denecher, J.: Un cas d'ulcère de la face posterieure de l'estomac chez un jeune homme de 16 ans., read before the Société de Chirurgie de Bordeaux et du Sud-Ouest, June 26, 1947.

390. Bolo, P. O.: Ulcero gastrica gigante de aspecto diverticular, Arch. argent. de enferm. d. ap. digest. y de la nutrición **22**:274, 1947.

391. Bats, M. E., and Lataste, M.: Ulcère gastrique chez un enfant de six mois, Arch. d. mal. de l'app. digestif **36**:417, 1947.

ulcer were found also to have a leiofibroma and a lymphosarcoma of the stomach, respectively.[392] A gastric ulcer developed acutely after irradiation of the hypophysis in a case of acromegaly.[393]

Benign Ulcer on Greater Curvature of Stomach.—Hussar [394] describes a case of ulcer of the greater curvature, proved benign histologically. The gastroscopic appearance of the lesion and its coexistence with a duodenal ulcer suggested the clinical diagnosis, in spite of its location. Gobeau and others [395] report another case in which the diagnosis was proved; Campbell [396] reports a third and fourth case of an ulcer proved benign histologically; in the latter, the ulcer healed after medical treatment. Cave [397] describes a fifth case, in which the lesion was associated with a duodenal ulcer.

Interesting Duodenal Ulcers.—A perforated duodenal ulcer in a 5 day old infant was associated with a hamartomatous growth of the tubercal region of the hypothalamus.[398] The simultaneous occurrence of duodenal ulcer and hyperthyroidism in 2 female identical twins is reported.[399] Coexistence of hyperparathyroidism and duodenal ulcer is described in the case of 2 male patients.[400] During a period of ten years, the same combination occurred in 12 cases among a series of 4,168 cases of peptic ulcer and 100 cases of nephrolithiasis. In 2 it could not be determined which of the two conditions had appeared first. In the remaining 10 cases, the ulcer preceded the nephrolithiasis in all, the interval varying from one to twenty-five years. Four cases of peptic ulcer complicating pregnancy, indicating that the combination may not be so rare as is generally believed, are reported.[401]

392. Limbosch, J.: Deux cas de tumeur gastrique rare avec ulceration concomittante, Acta chir. belg. **46**:682, 1947.

393. Fugazzola, F.: Acute Gastric Ulcer After Radiotherapy to the Hypophyseal Region in a Subject with Acromegaly, Policlinico (sez. prat.) **54**:293, 1947.

394. Hussar, A. E.: Benign Ulcer of the Greater Curvature with Case Report, Gastroenterology **9**:778, 1948.

395. Gobeau, C.; Bonte, G., and Dumez, L.: A propos de trois images d'ulcère de la grande courbure gastrique, Arch. d. mal. de l'app. digestif **36**:632, 1947.

396. Campbell, R. J. C.: Gastric Ulcer of the Greater Curvature, Brit. J. Radiol. **21**:146, 1948.

397. Cave, P.: Benign Ulcers of the Greater Curvature, Brit. M. J. **1**:1185, 1948.

398. Mossberger, J. I.: Perforated Duodenal Ulcer and Neoplasm of the Tuber Cinereum in the Newborn, J. Neuropath. & Exper. Neurol. **6**:391, 1947.

399. Robinson, H. M.: Duodenal Ulcer Concomitant in Identical Twins, Rev. Gastroenterol. **14**:489, 1947.

400. Bovarino Udaondo, C., and Castex, M. R.: Coexistence of Gastric and Duodenal Ulcer with Hyperparathyroidism or Nephrolithiasis, Prensa méd. argent. **35**:71, 1948.

401. Bralow, S. P.; Scheinberg, S., and Necheles, H.: Peptic Ulcer and Pregnancy, Am. J. Digest. Dis. **15**:137, 1948.

Primary Jejunal Ulcer.—A large ulcer located beyond the ligament of Treitz healed after medical treatment.[402]

Psychosomatic Relations.—The psychogenic aspects of peptic ulcer are discussed by Alexander,[403] Zane,[404] and others.[405]

In the case of a male patient with duodenal ulcer,[405d] the administration of enterogastrone was accompanied with a disappearance of acid from the gastric content. The induction of hostility at this time evoked much secretion of hydrochloric acid, which subsided when the stimulus was removed and the administration of enterogastrone continued. The reinduction of hostility failed to evoke a similar response after the patient had undergone transabdominal vagotomy. The role of hostility in the pathogenesis of peptic ulcer is discussed from a psychoanalytic point of view.

Ziegler [405e] presents the thesis that peptic ulcer may produce, or at least augment, anxiety symptoms and that healing of the ulcer may afford relief from the anxiety. In 1 case, severe anxiety and depression began at the same time as the ulcer distress. Despite the patient's being hospitalized for six weeks with daily psychiatric interviews, his condition continued to deteriorate until the ulcer was recognized and treated. Then, despite less intensive psychotherapy, the mental symptoms abated. Reversal of the usual concept of the order of areas affected is postulated, i. e., intestinal tract, vagus, hypothalamus and cortex.

Burden [406] found that peptic ulcer was less common among prisoners than among law-abiding citizens; it is not uncommon in the Negro race.

Vagal Hyperactivity.—Fredenhagen [407] and MacDonald [408] emphasize the role of vagal hyperactivity in the pathogenesis of peptic ulcer.

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402. Bonarino Udaondo, C.: Cabanne, E. A., and d'Alotto, V.: Ulcera simple del jejuno, Arch. argent. de enferm. d. ap. digest. y de la nutrición **22**:293, 1947.

403. Alexander, F.: Treatment of a Case of Peptic Ulcer and Personality Disorder, Psychosom. Med. **9**:320, 1947.

404. Zane, M. D.: Psychosomatic Considerations in Peptic Ulcer, Psychosom. Med. **9**:372, 1947.

405. (*a*) Gauss, H.: The Psychosomatic Aspects of Peptic Ulcer, Am. J. Digest. Dis. **15**:73, 1948. (*b*) Reese, J. A.: Peptic Ulcer—Is It a Psychosomatic Disease? Rev. Gastroenterol. **15**:159, 1948. (*c*) Gaskill, H. S.: Psychosomatic Relationships in Peptic Ulcer, Am. J. Roentgenol. **59**:100, 1948. (*d*) Szasz, T. S.; Levin, E.; Kirsner, J. B., and Palmer, W. L.: The Role of Hostility in the Pathogenesis of Peptic Ulcer: I. Theoretical Considerations with Report of a Case, Psychosom. Med. **9**:331, 1947. (*e*) Ziegler, D. K.: Amelioration of Anxiety Symptoms Accompanying the Healing of a Peptic Ulcer, J. Nerv. & Ment. Dis. **107**:276, 1948.

406. Burden, V. G.: Surgery of Peptic Ulcer in Prison, Rev. Gastroenterol. **15**: 208, 1948.

407. Fredenhagen, H.: Vegetative Constitutions in Pathogenesis and Treatment of Ulcers of the Stomach, Schweiz. med. Wchnschr. **77**:1251, 1947.

408. MacDonald, D.: Uncomplicated Duodenal Ulcer, Canad. M. A. J. **58**: 356, 1948.

Partial auriculoventricular block was attributed to increased vagal or parasympathetic tonus in 2 cases.[409]

Medical Treatment.—Jordan,[410] in an excellent paper, evaluates current diagnostic and therapeutic concepts. Further discussions of therapy are numerous.[411]

Antacids.—Batterman and Ehrenfield,[412] in a study of 159 cases, conclude that alkaline powders, magnesium trisilicate, so-called nonreactive aluminum hydroxide and aluminum phosphate gel are unsatisfactory in long-continued treatment. Hardt and Brodt,[413] as well as Kammerling and Steigmann,[414] recommend a mixture of aluminum hydroxide, magnesium trisilicate and mucin.

Metaphylene diamine (amberlite IR IV®), a synthetic resin with properties effecting anion exchange, is considered of value in the antacid therapy of peptic ulcer.[415] No evidence of toxicity had been noted at the time of writing in 60 cases in which 2 to 9 Gm. had been administered daily for six to eight months.[415a]

409. Björck, G.; Göhle, O., and Westman, C.: Partial A-V Block and Duodenal Ulcer, Acta med. Scandinav **130**:167, 1948.

410. Jordan, S. M.: Peptic Ulcer: A Diagnostic and Therapeutic Problem, Gastroenterology **9**:237, 1947.

411. Liebowitz, H. R.: Newer Aspects of Treatment of Peptic Ulcer, Bull. U. S. Army M. Dept. **8**:402, 1948. Larimore, J. W.: The Diagnosis and Treatment of Peptic Ulcer, South. M. J. **40**:572, 1947. Hirschberg, F.: Medical Treatment of Peptic Ulcer, Nord. med. **38**:771, 1948. Cunningham, T. D.; Mendenhall, J. C., and Mizer, F. R.: Treatment of Duodenal Ulcer, Rocky Mountain M. J. **44**:899, 1947. Ryan, J. M.: General Principles in the Treatment of Peptic Ulcer, Minnesota Med. **30**:742, 1947. Wilson, J. A.: Medical Treatment of Peptic Ulcer, ibid. **30**:960, 1947. Gordon, A. H.: The Treatment of Peptic Ulcer, Canad. M. A. J. **58**: 38, 1948. Green, D. M.: Present Status of the Peptic Ulcer Problem, Northwest Med. **47**:273, 1948. Boles, R. S.: Modern Medical and Surgical Treatment of Peptic Ulcer, J. A. M. A. **136**:528 (Feb. 21) 1948. Douthwaite, A. H.: Choice of Drugs in Treatment of Duodenal Ulcer, Brit. M. J. **2**:43, 1947.

412. Batterman, R. C., and Ehrenfield, I.: The Ambulant Treatment of the Peptic Ulcer Syndrome: The Comparative Effectiveness and Constipating Action of Antacids, Gastroenterology **9**:141, 1947.

413. Hardt, L. L., and Brodt, L. P.: Aluminum Hydroxide and Magnesium Trisilicate Plus Mucin in the Treatment of Peptic Ulcer, Arch. Surg. **55**:584 (Nov.) 1947.

414. Kammerling, E. M., and Steigmann, F.: Gastric Secretory Studies with Mucin Antacid Mixture, Am. J. Digest. Dis. **14**:381, 1947.

415. (*a*) Kraemer, M., and Siegel, L. H.: Synthetic Resin—New Antacid for Treatment of Peptic Ulcer, Arch. Surg. **56**:318 (March) 1948. Peters, A. G.: Anion Exchange Resin in the Treatment of Peptic Ulcer, Acta gastroenterol. belg. **11**:136, 1948.

Protein Hydrolysates.—The value of protein hydrolysates is emphasized in several papers.[416] Good results are reported in the cases of 18 ambulatory patients treated with protein hydrolysate as an adjunct to antacid therapy.[416b] Kenamore and his associates[416c] state:

> In a series of eighteen patients [with duodenal ulcer] fed an experimental mixture of protein hydrolysate and carbohydrate [dextrimaltose®] relief of pain was achieved in an average of 2.6 days. In a control group of thirteen patients on milk and cream feedings supplemented with the same carbohydrate the average time for relief of pain was 5.9 days. The diets in both groups were isocaloric, equal in quantity and served at the same hourly intervals.
>
> All of the experimental patients were in pronounced positive nitrogen balance; those in the control group were either in negative nitrogen balance or on the verge of it.

This finding is not surprising, since the patients treated with hydrolysate received 30 Gm. of nitrogen daily, whereas the control subjects were given only 6 Gm. Nitrogen balance studies were made by measuring the total daily urine output and reserving an aliquot of the twenty-four hour secretion. The aliquots were pooled with a preservative and the total nitrogen content determined at the end of one week and, again, during the next week. The amount of fecal nitrogen was estimated to be 10 per cent of the total nitrogen excreted. It is to be noted that the nitrogen intake and the nitrogen output in the feces were not measured directly. Riegel and others (Riegel, C.; Koop, C. E.; Drew, J.; Stevens, L. W., and Rhoads, J. E.: *J. Clin. Invest.* 26:18, 1947) demonstrate that a greater output of nitrogen occurs in the feces after the oral administration of protein hydrolysates than when the whole protein is fed.

The reviewers continue to regard with skepticism the published reports of superior results with protein hydrolysates. There is no question as to the desirability of maintaining nutrition at an optimum level; in the great majority of cases, this result can be achieved by the administration of an adequate diet. There is no conclusive evidence that deficiency of protein is a fundamental factor in the pathogenesis of ulcer, or that such a deficiency exists in the usual uncomplicated case; nor is there any evidence that patients with ulcer are incapable of utilizing whole protein as efficiently as the normal person. A recent paper by Woldman (*J. A. M. A.* 137:1289 [Aug. 7] 1948) indicates that protein hydrolysates do not efficiently neutralize gastric acidity; a similar conclusion may be drawn from the paper by Feller and Tidmarsh.[856]

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416. (*a*) The Management of Peptic Ulcer with Protein Hydrolysates, Conferences on Therapy, New York State J. Med. **47**:2111, 1947. (*b*) Rossien, A. X.: Protein Hydrolysate: Study of Effect on Peptic Ulcer Patients During One Year, Rev. Gastroenterol. **14**:623, 1947. (*c*) Kenamore, B.; Lonergan, W., and Shy, J. C.: Protein Hydrolysate Therapy in Peptic Ulcer, Gastroenterology **10**:177, 1948. (*d*) Steinberg, N.: A New Protein Hydrolysate for the Treatment of Peptic Ulcer, Rev. Gastroenterol. **15**:319, 1948.

Enterogastrone and Other Extracts of Stomach and Intestine.—Pollard and his associates [417] treated 28 patients with peptic ulcer with enterogastrone; 12 were given the concentrate orally in doses of 8 to 16 Gm. daily for periods up to eleven months; 16 patients were given intramuscular injections of 200 mg. of enterogastrone daily for periods up to nine months. The clinical results were not impressive. No changes were observed in the volume of gastric secretion in fasting patients, in the output of hydrochloric acid, in the concentration of pepsin or in gastric motility. These observations, together with the experience of the reviewers, indicate the need for further investigation of the effects of enterogastrone.

Mamie [418] reports that total extracts of the stomach and intestine (robuden®) were of value in treatment. Surkes [419] treated 79 patients with ulcer with bed rest, bland diet and a combination of oral and parenteral administration of robuden®; more than two thirds showed symptomatic improvement and healing on roentgenologic examination; no appreciable influence on gastric acidity was noted. However, the symptoms recurred in 63 per cent. The conditions of only 12 of 50 patients improved symptomatically during treatment with diet and a combination of oral and parenteral administration of robuden.® [420] The three reports are obviously unimpressive.

Roentgen Irradiation.—Galdos Larrú [421] utilized roentgen irradiation, as described by Palmer and Templeton in 1939, in 20 cases of peptic ulcer. The total depth dose was 2,000 r, given in ten fractional treatments. Pronounced clinical improvement was observed in all cases. Achlorhydria developed in 3. Anemia and diarrhea were noted in single cases. Despite the detailed individual case reports, information is lacking concerning the subsequent clinical course.

Miscellaneous Therapeutic Measures.—Conservative medical management, including large doses of vitamin B complex, is recommended.[422]

417. Pollard, H. M.; Block, M.; Bachrach, W. H., and Mason, J.: Treatment of Peptic Ulcer with Enterogastrone, Arch. Surg. **56**:372 (March) 1948.

418. Mamie, M.: Traitement de l'ulcère gastroduodenal par le robunden, Gastroenterologia **73**:157, 1948.

419. Surkes, A. W.: The Medical Treatment of Gastric and Duodenal Ulcer with Robuden, Schweiz. med. Wchnschr. **77**:455, 1947.

420. Bellomo, A., and Bologna, R.: Clinical Experiences in the Treatment of Gastric and Duodenal Ulcers with Gastric and Intestinal Extracts, Minerva med. **1**:540, 1947.

421. Galdos Larrú, M.: La rdaioterapia profunda en el tratamiento de la ulcera péptica, An. Fac. med., Lima **30**:233, 1947.

422. Kraucher, G. K.: Ein Beitrag zur Behandlung der Ulkuskrankheit, Wien. med. Wchnschr. **19**:211, 1948.

Gunther [423] apparently is impressed with the value of desoxycorticosterone acetate.

The inhibitory action of fat and fatty acids on motility, secretion and acidity has led Hyman [424] to assume that an increase in blood cholesterol may be beneficial in the treatment of ulcer. The reviewers are not convinced of the rationale of this procedure, nor are we impressed with the evidence cited in support of it. "Good results" are reported in 4 cases in which treatment was by continuous intragastric drip of penicillin in soda water [425]; thus penicillin comes to peptic ulcer, as apparently it must to all diseases! Warter and his co-workers [426] report relief of pain in 13 of 18 cases of gastroduodenal ulceration after infiltration of the sensory fibers of the pneumogastric nerves with 10 cc. of a 1 per cent solution of procaine hydrochloride U. S. P. Relief of pain is reported in a few cases after the intravenous administration of procaine hydrochloride U. S. P. (novocain®).[427]

Recurrences.—Three follow-up studies have been made.[428] In 192 cases of gastric ulcer and 495 cases of duodenal ulcer, in which a standard hospital medical regimen was continued for three to four weeks, primary results were good in 93.5 per cent.[428b] Results of a survey of the same persons seven to ten years later indicated a mortality of 3.9 per cent from ulcer and of 10.5 per cent from other diseases; patients were free of symptoms in 15.3 per cent of cases. The course was satisfactory in 31 per cent, fair in 19 per cent, and grave, i. e., severe relapse or death due to ulcer, in 40 per cent. Prognosis was poorer in cases of duodenal ulcer than in those of gastric ulcer because of more frequent relapses. Emotional stress, fatigue, lack of sleep, irregular hours of work and infection were thought to contribute more to relapse than improper diet.

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423. Gunther, L.: Aphorisms on Peptic Ulcer Seen in the Naval Service, U. S. Nav. M. Bull. **48**:207, 1947.

424. Hyman, M.: Some Considerations on the Possible Relationship of Cholesterol Metabolism to Peptic Ulcer, Am. J. Digest. Dis. **14**:235, 1947.

425. Young, R. W.: New Method of Treating Peptic Ulcers with Penicillin Gastric Drip, New Orleans M. & S. J. **100**:379, 1948.

426. Warter, J.; Fitzenkam, A.; Levy, A., and Rouillard, J.: Effect of Infiltration of Pneumogastric Nerves on Pains from Gastroduodenal Ulcer, Strasbourg méd. **108**:127, 1948.

427. Rumeau, P., and Dubarry, J. J.: Le traitement des ulcères gastroduodenaux par la novocaine intraveineuse, read before the Société de Chirurgie de Bordeaux et du Sud-Ouest, June 26, 1947.

428. (*a*) Kahrs, T., and Schrumpf, A.: The Results of the Medical Treatment of Peptic Ulcer, Rev. Gastroenterol. **14**:673, 1947. (*b*) Malmros, H., and Hiertonn, T.: The Life Cycle of Peptic Ulcer, Nord. med. **38**:744, 1948. (*c*) Flood, C. A.: Recurrence in Duodenal Ulcer Under Medical Management, Gastroenterology **10**:184, 1948.

A group of 233 patients with duodenal ulcer was followed for an average period of 6.9 years.[428c] Under medical management 21 per cent remained symptom free. The average rate of recurrence was once in 2.1 years. The incidence of recurrence for patients with hemorrhage was essentially the same as for the group as a whole. However, almost half the patients who had multiple hemorrhages showed further bleeding during the period of observation. Thirteen per cent of the entire group were subjected to operation because of persistent or recurrent pain, multiple hemorrhages or persistent pyloric obstruction. Although most patients of the series experienced recurrences, as a rule the symptoms were easily controlled by further treatment. Emotional trauma and feelings of insecurity were considered the commonest precipitating factors, but they were present also in persons who remained asymptomatic.

Complications.—Thompson [429] discusses the diagnosis and treatment of various complications of peptic ulcer.

Massive Hemorrhage.—A fatal hemorrhage in a man who had previously undergone gastroenterostomy for duodenal ulcer remained unexplained after autopsy.[430] Crohn and others [431] describe a series of 102 consecutive cases of gross hemorrhage originating in the upper alimentary tract. The diagnosis of duodenal ulcer was made in 59 cases and that of gastric ulcer, in 5; miscellaneous conditions were diagnosed in 16; these included hiatus hernia in 5, carcinoma in 4, esophageal varices in 2, and gastrojejunal ulcer, cardiospasm, regional ileitis, leiomyoma and myosarcoma in single cases, respectively. There was no detectable cause for the bleeding in 22 cases; subtotal resection of the stomach and part of the duodenum was performed in 2 cases of this group. In neither case was the cause of the hemorrhage determined, yet both patients remained well to the time of the report. Massive hemorrhage originated in an acute ulcer of the duodenum in the case of a patient who previously had undergone the removal of an ulcerated leiomyoma from the upper portion of the stomach.[432]

Jones [433] reviews in detail the subject of hematemesis and melena and analyzes a series of 687 consecutive cases, mostly of peptic ulcer,

429. Thompson, H. L.: Complications of Peptic Ulcer with Special Reference to Treatment, J. A. M. A. **136**:752 (March 13) 1948.

430. Jankelson, I. R.: Fatal Hematemesis of Unexplained Origin, Gastroenterology **9**:472, 1947.

431. Crohn, B. B.; Marshak, R. H., and Galinsky, D.: Repeated Gastric Duodenal Hemorrhages Without Discoverable Explanation, Gastroenterology **10**:120, 1948.

432. Thompson, H. L.: Recurring Melena in a Patient with Multiple Gastroduodenal Lesions, Gastroenterology **10**:551, 1948.

433. Jones, F. A.: Haematemesis and Melaena with Special Reference to Bleeding Peptic Ulcer, Brit. M. J. **2**:441, 1947.

studied from 1940 to 1947. The total mortality in the cases of ulcer was 7.8 per cent. The mortality rate increased from 2 per cent for persons under 45 to 21 per cent among patients of 70 or older. In discussing the role of operation, the author states that there is a small group of patients with chronic ulcer who show recurrent bleeding after admission, for whom "delayed emergency partial gastrectomy can be successful." The reduction in mortality is attributed to fewer recurrent hemorrhages, early feeding and liberal transfusions. Gastroscopy was successfully performed in 116 of 217 cases of the so-called "acute lesion group," in none of which was there roentgenologic evidence of ulcer. Gastric ulcers were recorded in 65 cases; "acute gastritis," in 6; atrophic mucosa, in 5; hypertrophic mucosa, in 10, and normal mucosa, in 30. Regarding treatment, the author emphasizes rest, mild sedation, early feeding, preparation for blood transfusion and use of the continuous milk drip and of ascorbic acid.

Wayburn [434] comments on the treatment in 71 cases, including 17 of hepatic cirrhosis and 43 of ulcer; a variety of causes were present in the remaining 11. Only 9 per cent of the patients with ulcer were under 40; 47 per cent were from 40 to 60, and 44 per cent were 60 or over. Thirty-one per cent of those with ulcer had a history of one or more previous episodes of bleeding; 41 per cent of the cirrhotic patients also had bled previously. The mortality rate was 14 per cent for the group with ulcer, and 59 per cent for the group with cirrhosis. The 6 fatal cases of ulcer included that of a 65 year old man who bled to death from an old duodenal ulcer despite pyloroplasty and vagotomy. The author concludes that conservative therapy is indicated in the overwhelming majority of cases with massive hemorrhage. Meulengracht [435] records a mortality rate of 2.5 per cent in a series of 1,031 consecutive cases of bleeding peptic ulcer in which treatment was by liberal feedings. Patients in all the fatal cases except 1 were over 40. Good discussions are presented by Gray [436] and by Andresen.[437]

Daly [438] treated 21 patients with hematemesis with 30 cc. of seventh-molar phosphate buffer of p_H 7.6, followed in five minutes with another 30 cc. of the buffer, containing 10,000 units of thrombin. In 12 cases a

434. Wayburn, E.: The Medical Management of Massive Upper Gastrointestinal Hemorrhage, M. Clin. North America **32**:328, 1948.

435. Meulengracht, E.: Fifteen Years' Experience with Free Feeding of Patients with Bleeding Peptic Ulcer, Arch. Int. Med. **80**:697 (Dec.) 1947.

436. Gray, S.: The Management of Patients with Massive Hemorrhage from Peptic Ulcer, M. Clin. North America **31**:1121, 1947.

437. Andresen, A. F. R.: Management of Gastric Hemorrhage, New York State J. Med. **48**:603, 1948.

438. Daly, B. M.: Use of Buffer Thrombin in the Treatment of Gastric Hemorrhage, Arch. Surg. **55**:208 (Aug.) 1947.

response was noted to the initial dose; in 5, only after two or more doses; in 4, surgical intervention was required. It is concluded that the administration of thrombin aids in the control of gastric hemorrhage when the content of the stomach is buffered.

The surgical aspects of massive hemorrhage are considered by Thompson,[439] McClure and Fallis,[440] and others; Haraldson [441] recommends transfusion and immediate operation for patients over 40. Gastric resection, for which a satisfactory result may be expected in 85 per cent of cases, offers the best protection against future hemorrhage, according to Holman.[442]

Perforation.—An analysis is made of the short term variations in the frequency of perforation in a large series of cases of peptic ulcer in which treatment was administered in the three main hospitals of Glasgow during the period from 1942 to 1945.[443] It is noted that the incidence of perforation remained comparatively uniform during the spring and summer; it decreased in the autumn but reached a peak in December. Perforation was uncommon on Sunday and Monday and during the night. The frequency of perforation increased toward the end of the morning, decreased in the early afternoon and again increased toward the end of the afternoon.

Among 101 cases of perforated peptic ulcer,[444] the perforation occurred after the patient's eating or drinking, in 14 cases; while the patient was in bed, in 27 (in 8 of these, the patient was in the hospital during therapy for ulcer); while the patient was walking or working, in 24, and after the patient had taken a laxative, in 9. The operative mortality was 18 per cent; the most important factor in this regard was a lengthened interval between perforation and operation.

Ramsey and Mosquera [445] report the case of a man of 78 who experienced an acute perforation of a duodenal ulcer, with fatal peritonitis, after a severe secondary burn of the skin. Sudden death, occurring only

439. Thompson, H. L.: Surgical Significance of Hematemesis and Melena, Arch. Surg. **56**:613 (May) 1948.

440. McClure, R. D., and Fallis, L. S.: Surgical Treatment of Bleeding Peptic Ulcer, Ohio State M. J. **43**:605, 1947.

441. Haraldson, S.: Prognosis in Conservative Treatment of Bleeding Peptic Ulcer, Nord. med. **38**:778, 1948.

442. Holman, C. W.: Further Observations on the Treatment of Bleeding Peptic Ulcer, Surgery **23**:405, 1948.

443. Jamieson, R. A.: Perforated Peptic Ulcer: Short-Term Variations in Frequency, Brit. M. J. **2**:289, 1947.

444. Moore, S. W., and Hendricks, R.: Late Results Following Perforated Peptic Ulcer, Surgery **23**:442, 1948.

445. Ramsey, T. L., and Mosquera, V. T.: Perforating Duodenal Ulcer Associated with Burns, Ohio State M. J. **43**:267, 1947.

minutes after perforation of a gastric ulcer,[446] remained unexplained at autopsy; peritonitis had not yet developed. In the case of a man of 26 under treatment for gastric ulcer, severe distention of the stomach suddenly developed, followed with perforation.[447] At operation it was observed that the perforation was not at the site of the gastric ulcer but involved an 8 by 9 cm. area in an apparently normal part of the anterior portion of the gastric wall near the cardia. Perforation of a duodenal ulcer in the case of a man of 58 [448] was followed one hour later with cardiac infarction and death. It is suggested that thrombosis occurred in the descending branch of the left coronary artery, already the seat of gross atherosclerosis, due to the combination of the shock of perforation with low blood pressure and poor blood flow. Bell, Owens and MacMurtrie [449] report two distinct perforations in a case of large duodenal ulcer. A duodenal fistula developed after operation, but the patient ultimately recovered completely. The authors state that a total of 43 similar cases have been reported.

Trinca [450] recommends simple closure without drainage, and the use of chemotherapy. Haeffner [451] reports 318 cases of perforating ulcer, 10 of which were complicated by the occurrence of severe gastric hemorrhage simultaneously with the perforation. In the 308 uncomplicated cases, the ratio of duodenal ulcer to gastric ulcer was 9 to 1 and the ratio of men to women was 15 to 1. Primary resection within six hours of the time of perforation is urged in all cases of chronic ulcer, provided the general condition of the patient is satisfactory. Closure should be combined with gastroenterostomy in cases of severe stenosis. Dumont [452] states that he prefers gastrectomy to simple closure.

Mackinnon's mortality rates [453] for the various procedures vary from 22.6 per cent to 33 per cent; Wingren [454] reports a reduction from 29.2

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446. Silverman, S.: Sudden Death from Perforated Gastric Ulcer, Lancet **2**:245, 1947.

447. Hillemand, P.; Leger, L., and Renault: Un nouveau cas de rupture spontanée de l'estomac, Bull. et mém. Soc. méd. d. hôp. de Paris **63**: 607, 1947.

448. Branwood, A. W.: A Case of Perforated Duodenal Ulcer and Cardiac Infarction, Brit. Heart J. **9**:263, 1947.

449. Bell, L. G.; Owens, J. C., and MacMurtrie, W.: Dual Perforated Peptic Ulcer and Duodenal Fistula, U. S. Nav. M. Bull. **47**:937, 1947.

450. Trinca, A. J.: Treatment of Acute Perforation in Peptic Ulcers, M. J. Australia **34**:385, 1947.

451. Haeffner, A.: Treatment of Free Perforating Ulcers, Wien. med. Wchnschr. **97**:388, 1947.

452. Dumont, R.: La gastrectomie dans les ulcères perfores, Acta chir. Scandinav. **95**:233, 1947.

453. Mackinnon, D. C.: Acute Perforated Gastric and Duodenal Ulcer, Minnesota Med. **30**:1253, 1947.

454. Wingren, J. E.: Perforating Ulcer, Nord. med. **37**:163, 1948.

per cent prior to 1941 to 7.4 per cent since then. Other authors [455] indicate agreement that a pronounced decrease in mortality has taken place with the advent of the antibiotic drugs. Successful closure of a perforated duodenal ulcer in the case of a man of 84 is reported.[456]

Bingham [457] states the conclusion that conservative treatment, including gastric aspiration, may be warranted in certain cases.

Plasma clot grafts and peritoneal grafts were found experimentally to be an unsatisfactory substitute for sutures.[458]

Anastomotic Ulcer.—Recurrent ulceration is discussed in several papers.[459] Among 62 cases of duodenal ulcer with gastric resection, gastrojejunal ulcer developed later in 2.[459c] Recurrent ulcer was noted in 3 cases after limited gastric resection and in 1 case after extensive resection; the original ulcer was duodenal or prepyloric.[459d] On the basis of an analysis of 38 cases, Doran [459e] concludes that the correct surgical treatment of anastomotic ulcer is Polya partial gastrectomy, with removal of at least three fourths of the stomach. Priestley and Gibson [459f] state that they advocate moderately high gastric resection, with removal of the pyloric antrum.

Gastrojejunocolic Fistula.—The roentgenologic features of recurrent jejunal ulcers and of jejunal fistulas are described in a well illustrated

455. Avent, C. H.; Patterson, R. H., and Chambers, J. M.: Acute Perforated Gastroduodenal Ulcer, South. Surgeon **13**:613, 1947. Larghero Ybarz, P.; Bosch del Marco, L. M.; Merola, L., and Giuria, F.: Perforated Gastric and Duodenal Ulcer, Arch. urug. de med., cir. y especialid. **31**:164, 1947. Treiger, P.: Acute Gastroduodenal Perforations, Am. J. Surg. **74**:459, 1947. Beechers, J.: La perforation aigue des ulcères gastro-duodenaux, Acta chir. belg. **46**:108, 1947. Hirshfeld, J. W.; Abbott, W. E., and Smathers, H.: Use of Chemotherapy as Possible Means of Reducing Mortality Rate in Perforated Peptic Ulcer, Am. J. Surg. **74**:54, 1947.

456. Ripstein, C. B.: Successful Closure of a Perforated Peptic Ulcer in a Man Eighty-Four Years of Age, Canad. M. A. J. **58**:281, 1948.

457. Bingham, D. L. L.: The Treatment of Acute Perforated Peptic Ulcer, Canad. M. A. J. **58**:1, 1948.

458. Bloom, J.: Plasma Clot Graft of Peritoneum for Perforations of the Stomach, Surg., Gynec. & Obst. **85**:155, 1947.

459. (*a*) Sharer, R. F.: Complications of Gastroenterostomy, Arch. Surg. **56**:528 (April) 1948. (*b*) Auguste, C.: Le diagnostic de l'ulcère peptique après gastrectomie, Acta gastroenterol. belg. **11**:131, 1948. (*c*) Skinner, H. L., and Duncan, R. D.: Gastric Resection for Duodenal Ulcer, Am. J. Surg. **75**:721, 1948. (*d*) Delannay, E.; Verhoeghe, M., and Lagarbe: Quatre cas d'ulcères après gastrectomie, Presse méd. **19**:222, 1947. (*e*) Doran, F. S. A.: The Surgical Treatment of Anastomotic Ulcer: An Analysis of Thirty-Eight Cases, Brit. J. Surg. **35**:377, 1948. (*f*) Priestley, J. T., and Gibson, R. H.: Gastrojejunal Ulcer: Clinical Features and Late Results, Arch. Surg. **56**:625 (May) 1948.

paper by Vandendorp and Bonte [460]; treatment is discussed by Barber and Madden,[461] and by Krueger.[462]

Multiple Complications.—Concomitant gastric and duodenal ulcers, hourglass deformity of the stomach, pyloric obstruction and massive hemorrhage are described in 1 case [463]; high gastric resection led to recovery.

Hypochloremia and Alkalosis.—The hypochloremia and alkalosis resulting from the loss of large amounts of gastric content may be associated with aciduria.[464] The desirability of treatment with a balanced solution of electrolytes, containing sodium, potassium, calcium and magnesium, is emphasized.

Karr and Hendricks [465] direct attention to the potentially toxic effects of intravenously administered ammonium chloride in the treatment of alkalosis.

Surgical Treatment and Results.—One hundred and fifty-four papers on gastric surgery are analyzed by Marshall and Gerber [466] in a useful review of the literature for 1946.

Priestley [467] states that approximately 85 per cent of all patients with duodenal ulcer can be treated medically. Massive hemorrhage failing to respond to medical management, recurrent hemorrhage, the cicatricial type of obstructive lesion, perforation and miscellaneous failures of medical management constitute indications for surgical intervention. Gastroenterostomy remains a procedure of value in many cases and entails less risk than gastric resection. Recurrent ulceration after gastric resection is less likely if a sufficient amount (two thirds to four fifths) of the stomach is removed.

Follow-up study of 279 patients on whom posterior gastroenterostomy was performed for peptic ulcer [468] indicates that approximately

460. Vandendorp, F., and Bonte, G.: L'ulcère peptique après gastrectomie: Diagnostique radiologique, Arch. de mal. de l'app. digestif **36**:558, 1947.

461. Barber, R. F., and Madden, J. L.: The Surgical Management of Gastrojejunocolic Fistula, Surgery **22**:657, 1947.

462. Krueger, J. T.: Gastrojejunocolic Fistula, Texas State J. Med. **43**:273, 1947.

463. Sanderson, E. R., and Player, G. S.: Hour-Glass Stomach, Northwest Med. **46**:689, 1947.

464. Van Slyke, K. K., and Evans, E. I.: The Paradox of Aciduria in the Presence of Alkalosis Caused by Hypochloremia, Ann. Surg. **126**:545, 1947.

465. Karr, N. W., and Hendricks, E. L.: Toxicity of Intravenous Ammonium Salts, Federation Proc. **7**:354, 1948.

466. Marshall, S. F., and Gerber, M. L.: Gastric Surgery: A Review of the Literature for 1946, Gastroenterology **10**:377, 1948.

467. Priestley, J. T.: Some Physiologic Aspects of the Surgical Treatment of Duodenal Ulcer, S. Clin. North America **27**:905, 1947.

468. Cooper, W. A.: End Results in the Treatment of Peptic Ulcer by Posterior Gastroenterostomy, Surgery **23**:425, 1948.

25 per cent may be expected to have recurrent symptoms within five years after operation; about 25 per cent of these can be managed successfully without further surgical measures. The mortality rate for posterior gastroenterostomy in 80 cases of cicatricial pyloric stenosis was 2.5 per cent; good results were obtained in all but 1 case.[469]

Ogilvie[470] reaffirms the view that gastrectomy for peptic ulcer must (*a*) reduce the secretion of acid, (*b*) ensure an adequate period of gastric digestion, and (*c*) direct the outflow from the stomach in a proper direction; these requirements are met by the Schoemaker type of Billroth I gastrectomy, with end to end gastroduodenal anastomosis. General discussions of the surgical treatment of peptic ulcer are presented also by Ransom,[471] Christaran,[472] Wells and Brewer,[473] and Walters, Gray and Priestley.[474]

According to Moore,[475] early operation, preferably partial gastrectomy, is indicated in patients over 55 with gross bleeding from peptic ulcer. Subtotal gastrectomy is also indicated in true cicatricial obstruction and when a gastric ulcer fails to heal within six weeks. Vagotomy may prove to be the procedure of choice in cases of intractable, nonbleeding, nonobstructed duodenal ulcer, and of jejunal ulcer. Preference for partial gastrectomy in the surgical treatment of peptic ulcer is expressed also by Seabrook,[476] Bruusgaard,[477] Grove and Rasmussen,[478] and Dumont.[479]

The mortality rate in 675 cases in which treatment was by resection was 3.6 per cent; 11 of the 24 deaths were the result of peritonitis.

469. Reid, H., and Marcus, R.: Posterior Gastroenterostomy for Organic Pyloric Stenosis: Review of End Results of Eighty Cases, Brit. J. Surg. **35**:304, 1948.

470. Ogilvie, H.: Gastrectomy, Lancet **2**:377, 1947.

471. Ransom, H. K.: Subtotal Gastrectomy for Gastric Ulcer: A Study of End Results, Ann. Surg. **126**:633, 1947.

472. Christaran, F. E.: Delayed Results in the Surgical Treatment of Duodenal and Gastric Ulcer, Rev. Asoc. méd. argent. **61**:888, 1947.

473. Wells, C., and Brewer, A. C.: The Surgery of Duodenal Ulcer, Brit. J. Surg. **35**:364, 1948.

474. Walters, N.; Gray, H. K., and Priestley, J. T.: Report on Surgery of the Stomach and Duodenum for 1946, Proc. Staff Meet., Mayo Clin. **23**:29, 1948.

475. Moore, F. D.: Current Practices in the Surgical Treatment of Ulcer, S. Clin. North America **27**:1071, 1947.

476. Seabrook, D. B.: Surgical Treatment of Peptic Ulcer, Rocky Mountain M. J. **45**:26, 1948.

477. Bruusgaard, C.: The Operative Treatment of Chronic Gastric and Duodenal Ulcer, Surgery **23**:161, 1948.

478. Grove, L., and Rasmussen, E.: The Proper Role of Subtotal Gastrectomy in the Treatment of Chronic Gastric and Duodenal Ulcer, South. M. J. **41**:255, 1948.

479. Dumont, R.: La gastrectomie dans les ulcères précoces, Acta gastroenterol. belg. **10**:63, 1947.

The mortality rate during the three and one-half years previous to the report was 0.74 per cent, compared to 5.4 per cent for the preceding decade.[480] At the Mayo Clinic, the hospital mortality rate in 241 cases of chronic duodenal ulcer in which partial gastrectomy was performed was 1.7 per cent. Total gastrectomies were performed in 24 cases of malignant lesions of the stomach, with a mortality rate of 16.7 per cent.[481] In a series of 182 cases of peptic ulcer in which gastrectomy was performed, recorded from 1940 to 1946, the over-all mortality rate was 4.6 per cent.[482] These results are in contrast to the mortality rate of 10 per cent in 61 cases in which treatment was by gastroenterostomy and to that of 14 per cent in 288 cases in which treatment was by gastric resection, recorded from 1929 to 1940. The author recommends subtotal gastrectomy as the elective surgical treatment for peptic ulcer. Steinberg [483] reports a mortality rate of 1.4 per cent in 280 consecutive cases in which "primary" gastrectomy was performed and in 4.3 per cent in 68 consecutive cases in which secondary gastrectomy was performed. Ramberg [484] found that the mortality rate in a group of 548 patients varied from nil among those from 16 to 30 to 17 per cent in those from 61 to 70 and 12.5 per cent in those from 71 to 80.

Visick [485] reviews 500 cases in which treatment was by a Polya type of gastrectomy, described as a "measured radical gastrectomy," which differs from the conventional gastrectomy in three respects: The area of stomach which remains can be measured and controlled with accuracy; the gastric remnant is extensively devascularized, and permanent achlorhydria results in 98 per cent of cases. Within 18 months after operation, recurrences developed in 3.7 per cent of cases with the conventional resection, whereas none occurred in those with the "measured" gastrectomy. The operative mortality rate was 0.7 per cent for patients under 40, 5 per cent for patients from 40 to 49, 5.8 per cent in patients from 50 to 59 and 7.1 per cent in patients over 60. Satisfactory results were obtained in 95 per cent of those cases followed from six months to twelve years.

480. Romcke, O., and Nicolaysen, K.: Treatment of Gastric and Duodenal Ulcers, Nord. med. **35**:1533, 1947.

481. Walters, W.; Counseller, V. S.; Waugh, J. M., and Clagett, O. T.: Report of Surgery of the Stomach and Duodenum for 1945, Proc. Staff Meet., Mayo Clin. **22**:345, 1947.

482. Pasman, R.: Late Results of the Surgical Treatment of Duodenal and Gastric Ulcer, Rev. Asoc. méd. argent. **61**:883, 1947.

483. Steinberg, M. E.: Gastrectomy for Peptic Ulcers, Rev. Gastroenterol. **15**:484, 1948.

484. Ramberg, R.: Stomach Resections for Ulcer, Nord. med. **37**:172, 1948.

485. Visick, A. H.: Measured Radical Gastrectomy, Lancet **1**:505 and 551, 1948.

Kennedy and his co-workers [486] studied the gastric stoma in 90 cases; a Polya type of resection had been performed in 83 and a modification of the Hofmeister operation, in 7. The size of the true gastric stoma remained the same, regardless of the type of gastric resection performed. Roentgenograms, taken four years after operation, indicated that the true stoma behaved in much the same manner as the pylorus with regard to peristalic activity.

Auguste and Paris,[487] in a study of 184 cases in which operation was by the Polya or Finsterer methods, noted that the decrease in acid occurred gradually. An investigation was made of the volume of acid secreted after subtotal gastrectomy and after vagotomy.[488] Free hydrochloric acid was absent in 15 of 31 cases with subtotal gastrectomy. The average amount of secretion in the course of one hour was 76 cc., a reduction of approximately 50 per cent. A much less dramatic reduction was observed after vagotomy; no indication is given, however, of the completeness of the vagotomy.

The results of gastrectomy in 615 cases are reviewed by Lake.[489] The mortality rate for carcinoma was 14 per cent; for anastomotic ulcers, 12 per cent; for duodenal and gastric ulcers, 5.7 per cent; for the last 130 cases in the series it was only 3 per cent. The incidence of anastomotic ulceration was slightly less than 1 per cent.

Sequelae of Gastric Resection.—Bonorino Udaondo and Castex [490] state that the absorption of calcium and phosphorus is impaired after gastrectomy; the lumbosacral-pelvic area is the chief site of osteoporosis.

Barnes [491] reports 3 cases of severe alimentary hypoglycemia after partial gastrectomy. He suggests that the level of blood sugar rises sharply after the ingestion of food, owing to rapid absorption of glucose. The repeated postprandial hyperglycemia ultimately leads to increased sensitivity to insulin. Gerrits and Rodbard [492] postulate neurogenic influences on the level of blood sugar as the source of the postresection syndrome. Postprandial hypoglycemia, the commonest complication, occurred in 17 of 45 consecutive cases.[493] The most

486. Kennedy, C. S.; Reynolds, R. P., and Cantor, M. D.: A Study of the Gastric Stoma After Partial Gastrectomy, Surgery **22**:41, 1947.

487. Auguste, C., and Paris, J.: Sur la rapidité de la disparition de l'HCL libre après gastrectomie, Presse méd. **49**:222, 1947.

488. Santy, P.; Marion, P.; Meley, J., and Schmuck, S.: Gastric Secretion After Subtotal Gastrectomy for Ulcers, Lyon chir. **43**:60, 1948.

489. Lake, N. C.: The Aftermath of Gastrectomy, Brit. M. J. **1**:285, 1948.

490. Bonorino Udaondo, C., and Castex, M. R.: Le trophisme osseux chez les gastrectomisés, Presse méd. **73**:847, 1947.

491. Barnes, C. G.: Hypoglycæmia Following Partial Gastrectomy, Lancet **2**:536, 1947.

492. Gerrits, W. B. J., and Rodbard, J. A.: Alimentary Hypoglycemia After Operations on the Stomach, Nederl. tijdschr. v. geneesk. **91**:3973, 1947.

493. Gilbert, J. A. L., and Dunlop, D. M.: Hypoglycemia Following Partial Gastroectomy, Brit. M. J. **2**:330, 1948.

effective method of treatment has proved to be a high fat diet, six meals daily and administration of one-half grain of ephedrine before the three main meals. Porges [494] states the opinion that the syndrome is caused by severe enteritis or jejunitis.

Faller and Kuhlmann [495] studied the late hematologic effects of gastric resection on 53 patients operated on between 1935 and 1940. Mild anemia was observed in approximately one-half the group. The tendency to anemia was three times greater among patients with ulcer of the lesser curvature than among those with pyloroduodenal ulcer. The anemia was not of the pernicious type; it was effectively corrected by the administration of iron.

Hypoproteinemia and Delayed Gastric Emptying after Resection.—Fretheim,[496] in a monograph of 122 pages, discusses in detail the plasma proteins in healthy persons and in patients undergoing gastrectomy. Pronounced hypoproteinemia is regarded as an important contributory cause of retarded wound healing. Efskind,[497] in a similar study, found that gastric retention was not more frequent in patients who had edema due to hypoproteinemia or even in those who had visceral edema at operation. Blood and plasma transfusions had no particular effect in reducing gastric retention. On the other hand, postoperative emptying difficulties in direct connection with gastric resection are attributed by Sandberg [498] to transient edema and to infiltration into the gastroenterostomy opening on the slit in the mesocolon. Bettman and Bloch [499] describe the case of a patient with an apparently well constructed gastroenterostomy who, two weeks after operation, experienced an almost complete obstruction of the stoma. Recovery occurred after five days of treatment, including rest in bed, sedation, continuous gastric suction and parenteral administration of fluids. The authors refer to several similar cases and recommend prolonged gastric suction as the best treatment.

Gardner and Hart [500] state the conclusion that none of the surgical procedures yields uniformly satisfactory results.

(To Be Continued)

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494. Porges, O.: The Jejunal Syndrome, Am. J. Med. **3**:177, 1947.

495. Faller, G., and Kuhlmann, J.: Repercussions of Gastric Resection for Ulcers on Formed Elements of Blood, Strasbourg méd. **107**:385, 1947.

496. Fretheim, B.: Post-Operative Hypoproteinemia After Gastrectomies, Acta chir. Scandinav. (supp. 130) **96**:1-122, 1947.

497. Efskind, L.: The Problem of Hypoproteinemia in Delayed Gastric Emptying After Stomach Resection, Acta chir. Scandinav. **95**:81, 1947.

498. Sandberg, I. R.: Postoperative Emptying Difficulties in Direct Connection with Gastric Resection, Acta chir. Scandinav. **95**:286, 1947.

499. Bettman, R. B., and Bloch, L.: Treatment of Delayed Opening of Stoma Following Gastric Resection, Gastroenterology **10**:143, 1948.

500. Gardner, C. E., Jr., and Hart, D.: The Surgical Treatment of Peptic Ulcer, Ann. Surg. **127**:1056, 1948.

Book Reviews

Racial Variations in Immunity to Syphilis: A Study of the Disease in the Chinese, and Negro Races. By Chester North Frazier and Li Hung-Chiung. Price, $2.50. Pp. 122. Chicago: The University of Chicago Press, 1948.

The authors have presented an analytic comparison of three syphilitic groups, the white and Negro races of Baltimore and the Chinese race of Peiping, China. Their study led them to conclude that, regardless of sex or race, the disease is essentially the same in all people. Syphilis was found to be a less serious disease in the Chinese than in either white or Negro races. This is demonstrated by the frequency of latency. The proportion of latency in the Chinese male approached that in the white female.

Early in the disease, the Chinese were found to react more violently than the white or Negro races. Chinese males were fifteen times as often the subjects of skeletal lesions and twice as often the subjects of symptomatic meningeal lesions as white males. However, as the infection progressed into the later stages, the excess of neural localization in the Chinese male was not sustained.

In the white race it was the neural structure which bore the weight of the disease, while in the Negro the cardiovascular system was more often involved. When lesions of the cardiovascular and the nervous system were taken together, the white race exhibited more serious pathologic changes than the Negro and the Negro more serious involvement than the Chinese.

Syphilis is milder in the female than in the male, as is seen by the preponderance of latency and the frequency of benign localization in the tertiary stage. The male type of the disease is vascular and neural and the female type is cutaneous, with a greater tendency to latency. The disease in the Chinese people was found to be more of the female type. This was seen in the early activity of the cutaneous and skeletal systems, the frequency of latency and in the relative infrequency of cardiovascular and neural syphilis.

The Chinese dietary habits are unique. If nutritional factors affect host resistance to Treponema pallidum or determine localization of the disease, the only evidence of this was found in the unusual susceptibility of the Chinese to the skeletal involvement. The authors conclude that since the Chinese, whether male or female, approached the milder pattern of female reaction to syphilis it is reasonable to assume that some inherent factor is responsible for this difference. In the Chinese there are certain qualities of bodily form and mental aptitude which indicate a strong feminine component of the bisexual fusion of this race.

Practice of Allergy. By W. T. Vaughan, M.D. Revised by J. H. Black, M.D. Second edition. Price, $15. Pp. 1132, with 333 illustrations. St. Louis: C. V. Mosby Company, 1948.

This volume is a comprehensive and authoritative source of both contemporary and historical information on the treatment of allergic disturbances. Originally written by the late Warren T. Vaughan in 1939, it has been revised and supplemented in the light of the many important developments that have occurred in the fields of clinical and experimental allergy in the intervening years by Dr. J. Harvey Black, associate editor of the *Journal of Allergy* and a practicing allergist. The internist as well as the allergist will find this volume understandable. It contains a wealth of material on clinical allergies, diagnostic procedures in cases of allergy and the physiology of allergy. Many chapters are devoted to food, to pollen and

other allergens which are inhaled and to allergic reactions in response to drugs, serums, bacteria, fungi and physical changes. There are also chapters on pharmacology, which include the subject of antihistaminics and miscellaneous data on the common and less common allergic diseases. Of great value for reference are the results of pollen surveys of most parts of the United States and adjacent areas, which were prepared for this text by O. C. Durham, the outstanding authority on this subject. Often the allergist is confronted with a patient from afar, whose seasonal allergic problems can be investigated intelligently when the physician knows the inhalant substances which the patient is likely to encounter in his own locality. This information is furnished, together with comparative pollen counts in different sections of the United States, Canada and Mexico, and thus recommendations may be given as to where to go to avoid the various pollens which cause hay fever.

Methods of diagnosis of allergic conditions and the shortcomings of each are presented well, and detailed information is given concerning various programs of desensitizations for allergies caused by inhalants, food and other allergens. Contact dermatitis is covered especially well.

If the volume was intended to be used as a textbook, it seems that perhaps the final chapters on allergic diseases, particularly on asthma, hay fever and other forms of allergic rhinitis and skin diseases, should have been made more extensive, at least to the extent of summarizing related material presented in detail in other portions of the book. For instance, description of the clinical picture of typical asthma, the common physical and laboratory findings and a summary of the principles of the allergic treatment as well as the nonallergic treatment would give the student or practitioner a better understanding of asthma than is to be found in the chapter on this subject.

The subject index does not seem entirely adequate. A chapter on the relationship of neurogenic factors to allergic diseases would seem worth while. James Holman has contributed a valuable chapter entitled "The Determination of Vital Capacity." More information on bronchoscopy in relation to asthma is desirable.

The book is well illustrated, and there are many valuable charts and diets included.

Lectures on the Liver and Its Diseases. By H. P. Himsworth, M.D. Price, $5. Pp. 204. Cambridge, Mass.: Harvard University Press, 1947.

The author of this monograph is well known in this country for his valuable contributions to the subject of experimental nutritional injury to the liver. The material presented in the book was first given in the form of the Lowell Lectures in March 1947 and represents the author's interest and long experience in the subject.

The first portion of the book concerns itself with experimental hepatic injury and gives an unusually complete account of the probable mechanisms by which various types of chronic lesions of the liver develop. There is an adequate discussion of the effect of experimental vascular lesions on the parenchyma of the liver and an excellent account of the nutritional factors which influence hepatocellular structure and function. To this has been added a consideration of the nutritional factors in injury of the human liver with some interesting data on this subject derived from study of African natives and orientals. In subsequent chapters the syndromes of both acute and chronic types of clinical hepatic failure are fully discussed and a new classification of diseases of the liver is presented. The sections of the book in which the various syndromes of hepatic disease are discussed are brief but adequate. The author pays his respects to Hanot's hypertrophic biliary cirrhosis and to "cholangeitis lenta" in some illuminating paragraphs. He has succeeded admirably in his attempt to transfer experimental data to a study of clinical disease of the liver, and the first portion of the monograph may well become

a standard reference textbook on the subject of experimental hepatic physiology, the material being well presented and admirably documented. This monograph is highly recommended, particularly to physiologists and those engaged in clinical investigation.

The Epithelia of Woman's Reproductive Organs. By George N. Papanicolaou, M.D. and others. Price, $10. Pp. 53, with 22 colored plates. New York: The Commonwealth Fund, 1948.

The microscopic appearance and the cyclic variability of the epithelia of woman's reproductive organs have been discussed in various publications. These articles have been widely scattered and in many languages. This monograph brings together and correlates this material for the first time. The studies are made complete by the additional knowledge added by each of the three authors—Dr. Papanicolaou, an anatomist, and Dr. Traut and Dr. Marchetti, both gynecologists with special training and interests in gynecologic pathology.

The epithelial structures of the ovary and the epithelia of the tube, endometrium, cervix and vagina are described in detail. Their variations during different stages of the ovarian and menstrual cycle are discussed and correlated. The cytology of the cells in smears prepared by vaginal, endocervical and intrauterine aspiration is also described and correlated with the previously described findings.

There are about 125 colored drawings and photomicrographs. They are representative and informative, and most are of excellent quality, although the reviewer wishes there were less drawings and more photomicrographs. The photomicrographs of endometria and endocervices suffer from the fact that the microscopic preparations of these tissues are not of the best quality. There is autolysis in some, and shrinkage artefacts in others. The latter may be due to the routine use of acetone dehydration.

This monograph will be of little interest to the general physician or medical specialist. To the histologist, pathologist and gynecologist it will be of interest and of reference value.

Bronchiogenic Carcinoma and Adenoma, with a Chapter on Mediastinal Tumors. By B. M. Fried, M.D. Price, $6. Pp. 206, with 118 illustrations. Philadelphia: Williams & Wilkins Company, 1948.

The author of this monograph is well qualified to write on the subject of bronchiogenic carcinoma. His observations are based on an extensive personal experience with pulmonary neoplasms, and he has assembled together in one volume the conclusions reached by many authorities who have written about bronchiogenic carcinoma. Dr. Fried devotes considerable space to a discussion of the increasing incidence of cancer of the lung and concludes that this increase is more apparent than real. The discussion of the histogenesis of bronchial cancer and its classification is orthodox. The existence of primary alveolar cell carcinoma is denied. A rather lengthy chapter is devoted to the various theories of cancerogenesis in general and the etiology of bronchiogenic carcinoma in particular. A special supplementary chapter deals with the relationship between pulmonary tuberculosis and cancer of the lung. Those chapters devoted to the clinical manifestations and to the metastasis of pulmonary carcinoma are well done. The author includes a special section on tumors of the superior sulcus. On the whole the reader gets the impression that the author is describing advanced disease. It might have been better to have devoted more space to differential diagnosis and the ways and means of recognizing bronchial cancer in its early stages. The author at times has placed undue emphasis on some of the less common manifestations of bronchiogenic carcinoma. An entire chapter is devoted to the subject of hypertrophic pulmonary

osteoarthropathy, which, in association with joint pain or possibly acromegalic symptoms, may occasionally be the outstanding sign of bronchiogenic carcinoma.

The chapter on laboratory diagnosis is good, and one is gratified to note that the author has given adequate attention to the isolation of cancer cells from sputum and bronchial secretions. Certainly, the study of desquamated cells in material raised by the patient or aspirated through the bronchoscope is the most important recent advance in the diagnosis of bronchiogenic carcinoma. The sections on treatment are brief. The limitations of radiation therapy are pointed out. The author's pessimism concerning surgical treatment is based on the failures of the past rather than on the hope of the future.

The chapter on bronchial adenoma summarizes the literature but does not solve the problems presented by this group of tumors. The section on mediastinal tumors is hardly adequate and might have been left out without detracting from the book. The author is at his best in his discussions of the various aspects of bronchiogenic carcinoma. Although it is hardly recommended for the student or general practitioner, the book should be of interest to all specialists in thoracic disease.

Neurology of the Ocular Muscles. By David G. Logan. Price, $6. Pp. 229. Springfield, Ill.: Charles C Thomas, 1948.

This book presents a general review of the clinical manifestations of the disturbances of the ocular motor system. It presents the neuroanatomic and neurophysiologic bases for the disturbances which are arranged according to objective signs in a detailed manner, with many diagrams and charts. Most of the well known syndromes involving the ocular muscles are given, with the localizing lesions.

The characteristics of the extraocular muscles as to the pharmacologic and physiologic reactions and the histologic observations are discussed.

The discussion of the general arrangement of the third, fourth and sixth cranial nerves is taken up, which is followed by a discussion of the supranuclear connections of the ocular motor system in which the lateral and vertical conjugate movements are presented and the supranuclear connections as affecting the lid movements.

Nystagmus is discussed in detail in the last chapter, and a workable classification is given.

The author refers frequently to the recent literature and discusses many of the problems that remain unsolved because of the difficulties of applying experimental work on animals to man.

The work is well done, but there is little help for the student who is interested in the usual problem of squint. Otherwise every ophthalmologist will enjoy having a copy of a book in which the common and rare neurologic syndromes are given and well analyzed.

News and Comment

GENERAL NEWS

Announcement of Annual Award by Kappa Delta Sorority.—The National Academy of the Kappa Delta Sorority has recently announced an award of $1,000 to be given annually for the most significant research in orthopedic surgery performed during the year.

The Committee on Scientific Investigation of the American Academy of Orthopaedic Surgeons will select the recipient of the award.

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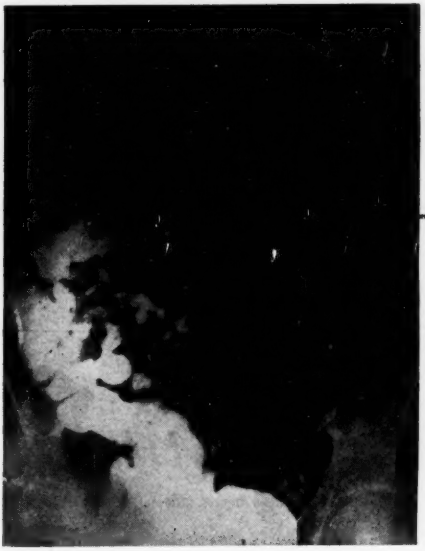

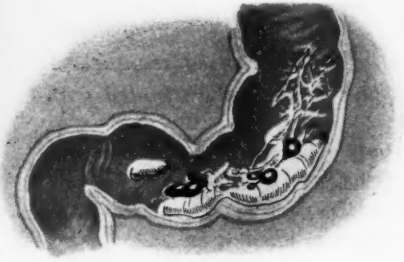

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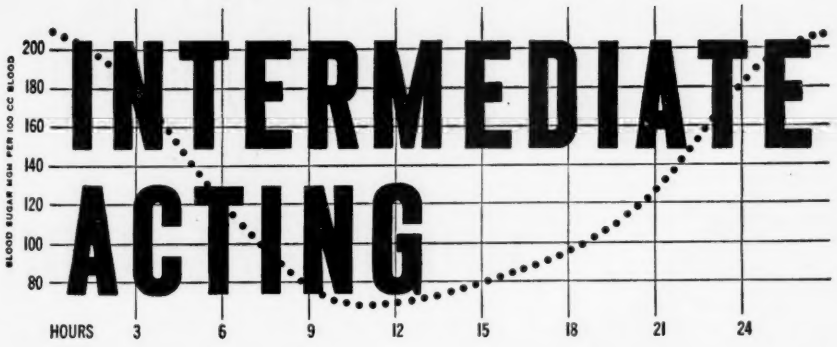

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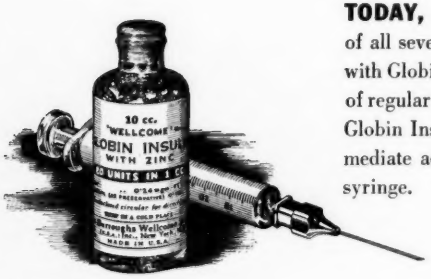

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1. Rohr, J.H., and Colwell, A.R.: Arch. Int. Med. 82:54, 1948.
2. Ibid Proc. Am. Diabetes Assn. 8:37, 1948

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